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CONTENTS

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The Dependence of the Genesis of Induced Skin Tumors on the Caloric Intake during Different Stages of Carcinogenesis*

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(Received for publication June 28, 1944)

In earlier investigations (11, 12) it has been shown that calorie-restricted diets inhibit the formation of tumors in mice. This effect has been demonstrated for the spontaneous breast tumor, induced skin tumor, induced sarcoma, and primary lung tumor. In those investigations the restricted diet was fed throughout the entire experiment. The experiments with spontaneous breast tumors were carried out on dba female mice, in which tumors normally begin to appear when the mice are 9 to 10 months old; in one of the experiments the restricted diet was instituted when the mice were, on the average, 9 months of age, *i. e.*, when tumors begin to appear, yet there was a pronounced inhibition of tumor formation. This suggested that the inhibitory effect on tumor formation may be dependent chiefly on caloric restriction during the period in which tumors appear, rather than in the previous period of carcinogenic preparation (12).

Tumors may arise long after exposure to the carcinogenic stimulus has ceased. Skin cancer of tar workers and bladder carcinomas of dye workers have often occurred many years after the persons exposed have given up employment in these industries. Results of experimental carcinogenesis are in agreement with these clinical observations. Such a separation of a carcinogenic stimulus and its result in terms of a tumor was shown as early as 1922 by Leitch (7), in experiments in which he tarred mice for a limited period.

The production of skin tumors by means of a limited application of carcinogenic hydrocarbon offers an excellent technic for separating arbitrarily the carcinogenic process into two stages. By terminating the paintings with the carcinogen just before tumors are expected, one may regard the period of carcinogenesis as being divided into:

I. The period of carcinogenic application; followed by

II. The period in which tumors appear. This paper is concerned with:

A. Determining in which of these periods caloric restriction [1] produces its main inhibitory effect on tumor formation, and

B. The possible value of these findings in understanding the mechanism of carcinogenesis.

METHODS

Four groups of mice, each on a different dietary regime, were used. Each group consisted of 50 pure strain dba [2] male mice, which were inbred in our laboratory and born within a span of a few weeks. The groups were equivalent as to age and weight; many of the animals in each group had litter mates in the other groups.

Two diets were employed: an *ad libitum* diet consisting of Purina dog chow, skimmed milk powder, and cornstarch; and a calorie-restricted diet consisting of the *same amounts* of dog chow and milk powder, but containing *no* cornstarch. Thus both diets contained equal quantities of protein, fat, vitamins, and minerals, and differed only in carbohydrate content.

* Presented at the Boston Meeting of the American Association for Cancer Research, April 1, 1942.

[1] Caloric restriction is a relative term. In this communication caloric restriction refers to a caloric intake approximately 60% of the *ad libitum* diet; only carbohydrate (starch) is restricted.

[2] The original stock was obtained from the Roscoe B. Jackson Memorial Laboratory.

The diets in grams per mouse per day had the following compositions:

	Ad libitum (A) gm.	Calorie-restricted (R) gm.
Dog chow meal	1.4	1.4
Skimmed milk powder	0.9	0.9
Cornstarch	1.9	0.0
	4.2	2.3
Average daily food consumption,	3.8-4.1	2.3
(Computed from manufacturers' analyses)		
Protein	0.62	0.62
Fat	0.08	0.08
Ash	0.16	0.16
Carbohydrate	2.93	1.22

A week's supply of the weighed dietary constituents was mixed with sufficient water to form an easily molded mash, cut into equal blocks, and stored in a refrigerator. The mice were fed daily. Those on the restricted diet consumed all the food given them. The actual food consumption of the *ad libitum* group was estimated by weighing back each week the food left in the cages. All animals had free access to water.

The animals consuming the *ad libitum* diet were housed 5 in a cage. Each group of 5 mice on the restricted diet was kept in 2 cages; at the bi-weekly weighings the lighter animals were placed in one cage, the heavier in the other. Thus the restricted animals competed with others of the same order of weight and, over the long period of restriction, consumed approximately equal quantities of food.

Skin tumors were induced by applying 1 drop of the carcinogen solution with a dropping pipette twice weekly to the skin of the interscapular region. A 0.3 per cent solution of 3,4-benzpyrene in benzene was used, each drop containing approximately 0.05 mgm. of the carcinogen.

At 2 week intervals the animals were inspected for neoplasms and weighed. The tumors were recognized as papillomas or carcinomas by their gross appearance and by palpation. None of the papillomas regressed. About 80 per cent were ultimately converted into carcinomas. Most of the remaining 20 per cent is accounted for by those in mice that died before the conversion took place or by papillomas that arose too late in the experiment for the change to be observed. Since the exact time of conversion is not recognizable the tumor count and time of appearance refer to the first tumor that each mouse developed.

All animals were examined post mortem. Histological examinations were made of many lesions selected at random, and of all those about which doubt existed; the results of the histological studies indicated that the gross examinations were reliable. Percentages of tumor formation were computed on the basis of the number of animals alive in the group (effective total) at the time the first tumor appeared in the experiment, and also on the basis of an adjusted total, described by Bryan and Shimkin (3), that accounts for the deaths of nontumor animals during the period in which tumors appear.

EXPERIMENTAL

Two of the 4 equivalent groups of mice, 10 weeks of age, were placed on the *ad libitum* diet, while the other 2 groups were given the calorie-restricted diet. After 4 weeks, there was applied to all the mice of the 4 groups the first of 19 semi-weekly applications of the carcinogen. No tumors had appeared at the time the application of the carcinogen had been completed.

Two days after the final application of the carcinogen the following dietary changes were made: One of the groups being fed *ad libitum* was continued on this diet while the other was transferred to the calorie-restricted diet; similarly, one of the groups being fed the calorie-restricted diet was continued on this ration while the other was transferred to the *ad libitum* diet. The experiment was then continued for 52 weeks, during which period tumors appeared. Thus the 4 groups had different sequences of diet: *ad libitum*—*ad libitum* (AA), *ad libitum*—restricted (AR), restricted-restricted (RR), and restricted—*ad libitum* (RA). The changes in diet (AR and RA) were made after the application of carcinogen was terminated, and before tumors had appeared.

In Fig. 1 the mean weight curves of the mice in each of the 4 groups are given. After termination of the application of the carcinogen the mean weights of the 2 groups, RA and AR, whose diets were changed, begin to approach the corresponding mean weights of groups AA and RR respectively. The adjustment occurs over a transition period of weeks.

Table I shows the cumulative tumor counts in the 4 groups at various periods of the experiment. It is to be noted that at the termination of the experiment 32 tumors had arisen in the AA group, 16 in the AR, 11 in the RR, and 24 in the RA. "Per cent tumors" are given both as percentages of the effective total and of the adjusted total. Both methods of computing the percentage of mice with tumors give comparable figures, indicating that the differences are not due to unequal distributions of deaths (in time or number) among the groups.

In Fig. 2 the tumor percentages (cumulative) are presented graphically. It can be seen that the RA curve begins somewhat later but tends to approach the AA curve. Likewise the AR curve tends to parallel the RR

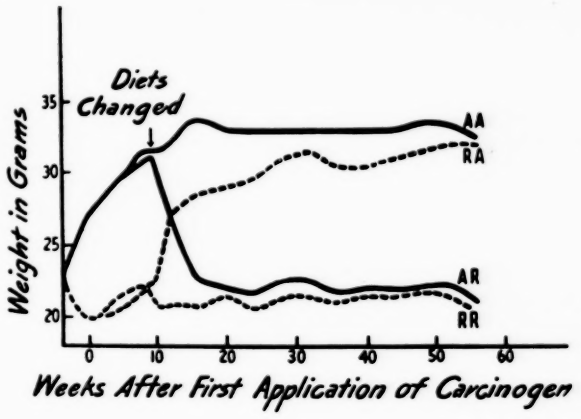

FIG. 1.—Mean weight curves of the groups on the 4 different caloric sequences.

The two groups, AA and RA, that were fed *ad libitum* during the period of tumor appearance, have a tumor incidence of about the same order, suggesting that the carcinogenic agent produces the initial fundamental changes regardless of the diet—restricted or *ad libitum*—fed during the period of carcinogenic application. Based on this conclusion it is of interest to make the following comparisons: AA and AR, which shows that caloric restriction in the period of tumor appearance inhibits the genesis of tumors; AR and RR, which indicates that the inhibition of tumor formation observed in the latter group is principally due to caloric restriction during the period of tumor appearance; and RA and RR, which, conversely, reveals that full feeding in the period of tumor appearance favors the genesis

TABLE I: RELATIONSHIP OF TUMOR INCIDENCE TO THE PERIOD OF CALORIC RESTRICTION

Group	Diet in period of: Painting (10 weeks)	Diet in period of: Tumor formation (52 weeks)	No. of mice (effective total)	CUMULATIVE TUMOR COUNT: Weeks after first application of carcinogen 10	14	20	26	32	38	44	50	56	62	No. of mice tumor-free and alive at end of experiment	PER CENT TUMORS of effective total	PER CENT TUMORS of adjusted total
AA	*Ad libitum*	*Ad libitum*	49	0	8	13	17	21	23	27	30	32	32	1	65	69
AR	*Ad libitum*	Restricted	50	0	0	1	4	9	10	11	14	16	16	26	32	34
RR	Restricted	Restricted	50	0	0	2	2	5	5	7	9	11	11	26	22	24
RA	Restricted	*Ad libitum*	50	0	0	1	4	4	10	16	22	23	24	9	48	55

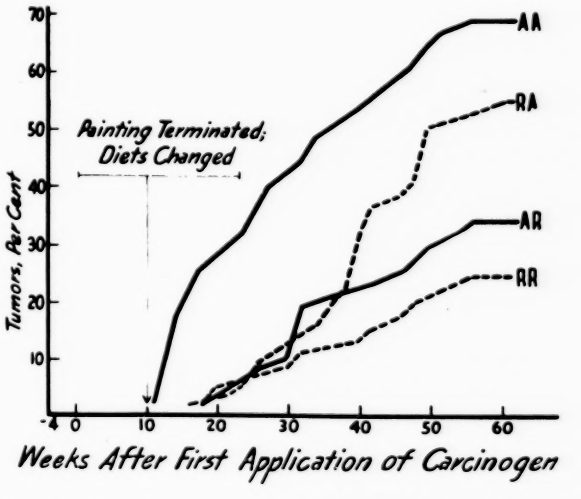

FIG. 2.—Cumulative percentages of induced skin tumors (on basis of adjusted totals) in each of the 4 experimental groups.

curve. Thus, the 4 experimental groups can be divided, from the viewpoint of tumor incidence, into low-tumor groups, RR and AR, and high-tumor groups, AA and RA.

Comparison of AA and RR clearly shows the significant inhibitory effect on tumor formation when there is caloric restriction throughout the entire period of carcinogenesis. The degree of inhibition in group RR must be regarded as the base line in considering the effects produced by restricting the diet in only one period.

of tumors. The results of these experiments are best explained by assuming that the process of carcinogenesis is divided into two phases: (a) an initiatory or pre-neoplastic stage, which under suitable conditions leads to (b) a developmental or neoplastic stage that culminates in a perceptible tumor. Caloric restriction has little or no effect in preventing the initial stage, while it distinctly inhibits the fruition of the neoplastic stage.

DISCUSSION

The induced skin tumor was chosen for these studies because its use provided excellent conditions for this particular type of investigation. An exact and equal amount of carcinogen could be applied to the animals of both the *ad libitum* and restricted groups, and discontinued before dietary changes were made. Furthermore, the carcinogen and its conversion products, as judged by fluorescence studies (1; 4-6; 10; 13; page 474), are known to disappear from the skin within a short period after the last application of the carcinogen. These two conditions are not obtained as experiments are usually performed, with either the sarcoma induced by carcinogenic hydrocarbons or the spontaneous breast tumor.

Our experiments permit the inferences: (a) that the initial fundamental changes due to the application of a carcinogen to the skin occur essentially to the same extent regardless of whether the animals are on

a full or calorie-restricted diet, and (b) that it is the caloric regime during the period in which tumors appear that determines, to a large degree, whether or not a tumor will eventuate. Although the qualitative results are definite, certain aspects of the present experiment should be considered. A particularly important factor in the differences in tumor incidence between AA and RA, and between RR and AR, may be that under the conditions of our experiment there is only a very short interval between the time of the reversal of diets (and termination of carcinogen application) and the appearance of the first tumor. Consequently, during at least part of the period in which tumors appear the weights of the RA mice are less than those of the AA mice; conversely, the weights of the AR animals are higher than those of the RR animals. These relationships can be modified by a proper choice of potency, quantity, and duration of carcinogen application.

One may conclude from the experiment reported in this communication that carcinogenesis can be divided into at least 2 distinct phases: (a) a stage of preparation, latency, initiation, or pre-neoplasm, in which the cells become prepared or biased toward forming a tumor; and (b) a stage of development or formation that eventuates in a perceptible tumor.

The carcinogen initiates pre-neoplastic changes regardless of whether the animals are on an *ad libitum* or calorie-restricted diet. In contrast, the *ad libitum* diet favors the development of these initial changes into perceptible tumors, while the calorie-restricted diet acts either by reversing these initial changes or preventing their development in many of the animals. These interpretations are given added significance by their agreement with the work reported by Rous and his associates (8, 9), and by Berenblum (2).

Rous and Kidd (9), and MacKenzie and Rous (8), have shown that when a carcinogenic tar is applied to rabbit skin many more epidermal cells are rendered pre-neoplastic than declare themselves by forming tumors. Cells that had been conditioned or biased by tar painting were encouraged to form tumors by wound healing or the application of turpentine. The nonspecific stimulation of wound healing acted as the deciding influence in causing cells that had been "initiated" or "prepared" by tarring to eventuate into perceptible tumors. The authors bring out the need for a sharp distinction between the forces that induce neoplastic change (initiation or inception) and those that determine, or prevent, its realization in terms of a tumor (formation).

Investigations by Berenblum (2) on the augmentation of carcinogenesis by means of noncarcinogenic agents (cocarcinogenic action) have resulted in significant observations and interpretations. This investigator studied the effect exerted on the formation of skin tumors (induced by 3,4-benzpyrene) by croton resin (or turpentine) applied prior to, during, or after the application of the carcinogen. The use of croton resin prior to benzpyrene application had little or no demonstrable effect; its application concurrent with benzpyrene throughout the experiment led to a pronounced increase in the formation of tumors; and its use after a limited period of benzpyrene application also resulted in a pronounced increase in the formation of tumors. This suggests that croton resin produces its principal effect when applied during the second stage (developmental) rather than during the initial (preparatory) stage.

Although the precise cellular changes that eventuate in a tumor are not known, it has been possible to distinguish 2 well-defined stages of carcinogenesis. The first stage of initial changes is brought about by specific carcinogenic agents. A consideration of the 3 distinct and different investigations suggests that these initial changes, once present, may then be favored by certain factors, resulting in tumors; or not favored, resulting in lack of development or possibly regression of these initial changes. Rous and his associates have shown that wound healing favors and encourages tumor formation from these biased cells. Berenblum has shown that croton resin has a similar effect. Both have found that turpentine has comparable properties. Our own work indicates that an adequate caloric intake favors the formation of tumors from the biased or conditioned cells, while a diet that is calorie-restricted distinctly inhibits the development of tumors. Thus, in the skin of an animal, the changes brought about by a carcinogenic agent can be so altered by three distinct and diverse means (wound healing, croton resin, or a normal caloric intake) that considerably more tumors develop than in the absence of these factors.

All 3 investigations, those of Rous and his associates, Berenblum, and our own, demonstrate that carcinogenesis may be considered to be divided into at least 2 distinct phases: (a) a stage variously designated as initiation, inception, latency, preparation, or pre-neoplasm, produced by the carcinogenic agent; and (b) a stage of development, formation, or epicarcinogenesis, in which these initial changes result in a perceptible tumor even without the continued application of the carcinogenic agent. It is of significance that entirely different means—wound healing, croton resin, and caloric restriction—can affect the developmental stage; whereas it seems likely, though not definitely proved, that these same agents have little or no effect upon the initiation stage.

SUMMARY

In earlier experiments it has been shown that calorie-restricted diets inhibit the formation of various types of tumors in mice. Although the restricted diet had been fed throughout the entire experimental period, there were observations suggesting that the inhibition may have been produced principally during the period in which tumors appeared, rather than in the preceding period of initiation.

The production of skin tumors in mice by means of a limited application of carcinogenic hydrocarbon permitted the arbitrary separation of carcinogenesis into two periods or stages: initiation and development. The results, summarized below, were obtained by feeding various sequences of an *ad libitum* and calorie-restricted diet to 4 groups of mice that were given equal applications of carcinogen.

Group	Diet in period of painting (10 weeks)	Diet in period of tumor formation (52 weeks)	Tumors, per cent (Adjusted)
AA	*Ad libitum*	*Ad libitum*	69
AR	*Ad libitum*	Restricted	34
RA	Restricted	*Ad libitum*	55
RR	Restricted	Restricted	24

These data demonstrate that carcinogenesis can be divided into 2 distinct phases:

I. A stage of preparation or initiation in which the normal cells become prepared or biased toward forming a tumor, and

II. A stage of development or formation that eventuates in a perceptible tumor. Furthermore, it is shown that:

A. The initial fundamental changes due to the application of a carcinogen occur regardless of whether the mice are on a full or calorie-restricted diet, and

B. A full diet promotes the development of tumors from these initial changes, while a calorie-restricted diet inhibits such development.

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The Importance of Differential Consideration of the Stages of Carcinogenesis in the Evaluation of Cocarcinogenic and Anticarcinogenic Effects

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This communication is an attempt to clarify and extend the concepts dealing with certain extrinsic or intrinsic factors that augment or retard carcinogenesis. Before discussing carcinogenesis it may be helpful to differentiate again between carcinogenesis and the subsequent growth of a tumor.[1] Carcinogenesis implies the initiation of a neoplasm by a tumor-producing agent acting on normal tissue. Once the tumor is of microscopic size, even before it is perceptible on gross examination, carcinogenesis can be assumed to have been completed; the multiplication of the new tumor cells represents growth. The differentiation between genesis and growth is based both on morphological considerations and on the experimental observation of factors that encourage or inhibit carcinogenesis, while they have little or no influence on the growth of the tumor. Thus it is of experimental and possibly of clinical importance to distinguish between the *genesis* of a neoplasm from normal tissue, and the *growth* of such a tumor, or of tumor implants. Nevertheless one still finds references in the literature to the effects of a particular agent or procedure, without regard to the difference between genesis and growth.

A parallel situation, dependent on the recognition of distinct stages in carcinogenesis itself, has developed more recently. On the basis of experimental data and suggestions by Rous and his associates (30, 36), Berenblum (10), Tannenbaum (44), and the earlier work of others (19-21), and for experimental and possibly clinical purposes, it appears desirable to consider differentially the recognizable stages of carcinogenesis.

Stages of carcinogenesis.—In extensive morphological studies many workers have demonstrated that when a chemical carcinogen is applied repeatedly, or even once, to the skin of a susceptible animal a series of changes antecedent to tumor formation takes place. In the main these include epithelial hyperplasia and increase in nuclear and nucleolar size; dermal alterations involving the hair follicles, sebaceous glands, collagen and elastic fibres, and inflammatory cells; and definite chemical changes in the epidermis (13-15, 18, 32, 34, 35, 39, 41, 49). These may be only coincident with, or may themselves actually be, the lesions that have been referred to as *initiation* or *pre-neoplasm*. For even though the application of carcinogen is discontinued before tumors are expected, papillomas may develop in the pre-neoplastic site. It is therefore believed that the first stage, either gradually or abruptly, goes over into the second stage of tumor *formation* or *neoplasm*.

In a previous communication (44) it was pointed out that biological experiments of diverse nature support this view: That carcinogenesis may be divided into at least two distinct stages: (a) a stage of preparation, latency, initiation, or pre-neoplasm, in which the normal cells become biased toward forming a tumor; and (b) a stage of development, formation, or neoplasm, which eventuates in a perceptible tumor. In this respect our conclusions agree with those of Rous and his associates, Berenblum, and others.

Berenblum (10), in discussing the genesis of skin tumors, also includes the concept of metacarcinogenesis (the conversion of a benign into a malignant tumor). We prefer to omit discussion of this concept, since the relationships of benign to malignant neoplasms are not clear. In the case of the skin, does the malignant cell develop from a papilloma cell or from a normal cell that is converted directly into a malignant cell? Is the carcinogenic agent responsible for this conversion, or is the change produced by the growing papilloma? Often the malignant tumor seems to be formed directly, and not from a benign papilloma. Moreover, other

[1] The distinction between genesis and growth of a tumor may be likened, in a broad sense, to the distinction between conception and growth of a fetus. In both phenomena there may be no general agreement regarding the exact limits of component parts of the complete processes, or even whether such exact limits exist. Nevertheless, for the discussion of clinical and experimental observations, such separations have validity and usefulness.

malignant neoplasms in animals, such as the spontaneous breast adenocarcinoma and induced sarcoma of the mouse, seem to develop directly and not through an intermediary benign tumor. Consequently, metacarcinogenesis will be omitted from this discussion and carcinogenesis will be regarded as consisting essentially of the two stages: (a) *pre-neoplasm* (initiation), and (b) *neoplasm* (development).

Anticarcinogenesis and cocarcinogenesis.—In recent years substances have been found that either promote or inhibit the development of skin tumors when they are applied concurrently with a carcinogen. Berenblum (4) applied the term "anticarcinogen" to dichlorodiethylsulfide (mustard gas), which inhibits the formation of tumors when applied concurrently with the carcinogen, and Shear (38) suggested the term "cocarcinogen" to describe the augmenting effect of the basic fraction of creosote oil. Both stressed the fact that these substances, by themselves, do not initiate tumors,[2] but under optimal conditions either inhibit or promote their induction by carcinogens. Later these two investigators reported further experimental work along these lines (6, 7, 9, 12, 37) and Berenblum adopted Shear's term "cocarcinogen" to describe the augmenting effect of croton resin.

One gets the impression from Berenblum's paper (10) that he considers that anticarcinogenic and cocarcinogenic actions influence the conversion of the pre-neoplastic stage to the neoplastic stage (epicarcinogenic action—Berenblum), though his definition and discussion of cocarcinogenesis also imply that it may exert its effect at other times. However, our experimental results, as given both in the preceding and succeeding communications (44, 45), coupled with a critical evaluation of the literature, indicate that it may be possible to differentiate between the effects of a cocarcinogen (or anticarcinogen) in each of the two distinguishable stages of carcinogenesis.

In brief, it is our thesis that cocarcinogenic and anticarcinogenic agents may involve either the pre-neoplastic or neoplastic stage separately, and that the mechanism and nature of the effect may be entirely different during these two stages. It is possible that a particular means or substance may have one effect, cocarcinogenic, anticarcinogenic, or none, on the development of the pre-neoplastic stage; and another effect, cocarcinogenic, anticarcinogenic, or none, on the conversion to the neoplastic stage.

It has been demonstrated that wound healing (30, 36), croton resin (10), and free caloric intake (44) will all promote the production of skin tumors at sites already rendered pre-neoplastic by the previous application of suboptimal doses of carcinogen for a limited period, evidence that the augmenting effect evokes and/or maintains the neoplastic stage. It is likely that the same agents have little or no effect upon the development of the pre-neoplastic stage; thus these means of promoting carcinogenesis can be considered cocarcinogenic actions that affect principally the development of the second or neoplastic stage of carcinogenesis.

On the other hand, certain substances exert their principal influence when applied during the period of limited carcinogen application. It is well known that the potency of a carcinogen is dependent on the nature of the solvent used and the condition of the skin, as well as on other experimental factors. For example, when 0.5 per cent strength of 1,2,5,6-dibenzanthracene was applied in various solvents it was found that tumor production was highest with chloroform, lower with oleic acid, and lowest with liquid paraffin (46). Again, ether or acetone, for a specific concentration of carcinogen, effects a much higher production of tumors than benzene (16, 42), and the addition of as small an amount of paraffin as 2 per cent increases the effectiveness of both ether and benzene (16). On the other hand, dissolving the carcinogen in mouse fat or lanolin rather than in benzene results in a considerable reduction of tumor formation (31, 40). There are many more examples of the now established fact that the physical and chemical nature of the solvent can greatly influence the response to a given concentration of a carcinogen.

In addition, there is much experimental evidence that application to the treated area of various solvents and agents before or between applications of carcinogen may considerably affect tumor formation. Watson and Mellanby (47) review the early work on this subject, and in their own experimental data clearly establish the accelerating effect of mouse fat and olive oil under these conditions, and an increased tumor incidence due to preliminary application of mouse fat has been confirmed (31). Baumann and his associates have also contributed valuable data (26-28).

The same wide variation occurs in sarcoma production when different solvents are used in the subcutaneous, intramuscular, or intraperitoneal injection of carcinogens. Early reports by Peacock (33), Watson (48), and Berenblum and Kendal (8) emphasize this. For example, a carcinogen in homologous fat produces fewer tumors than when dissolved in lard or sesame oil. There is considerable literature on this subject, which has been adequately surveyed by Burdette and Strong (11) and by Dickens and Weil-Malherbe (22). More recently Leiter and Shear (29) have reviewed certain aspects of this subject, and in extensive experimentation have compared tricaprylin

[2] An agent, administered alone, may have a slight carcinogenic effect, but this does not preclude the possibility that it may possess a strong cocarcinogenic or anticarcinogenic action.

and various lard fractions. They report: "In comparison with tricaprylin as the control vehicle, lard residue produced a striking retardation of tumor production whereas lard filtrate promoted it. Further fractionation indicated which components may be responsible for the promoting action and demonstrated that the retarding influence resides in the glyceride fraction richest in saturated fatty acids of high molecular weight."

The effectiveness of a carcinogen is therefore dependent, among other factors, on the nature of the solvent, and, with regard to skin tumors, can be modified by the addition of certain agents to the skin before or between applications of the carcinogen. In other words, solvents and other agents may exert a profound cocarcinogenic or anticarcinogenic influence during the initiation or pre-neoplastic stage. In contrast, these same solvents and agents may have little or no effect when applied after a limited application of carcinogen, *i.e.,* during the developmental or neoplastic stage.

Little is known about the fundamental cellular changes of carcinogenesis, in either its pre-neoplastic or neoplastic stages. However, it is obvious that solvents or agents that augment or inhibit in the pre-neoplastic stage must do so in the presence of the carcinogen (or its conversion products). On the other hand, cocarcinogenic and anticarcinogenic actions in the neoplastic stage may occur principally in the absence of carcinogen, since it has been shown that this disappears from the skin within a few weeks after the last application (2, 23-25, 39, 43 page 474).

It is likely that a solvent or agent applied during the pre-neoplastic stage exerts its main effect on the rate and amount of carcinogen absorbed into the skin; or, in the case of sarcoma production, the rate of removal or diffusion from a subcutaneous site. This mechanism may be considered a physical or solvent influence on the effective dosage of the carcinogen. On the other hand, some agents, whether applied after a limited or throughout a prolonged application of a carcinogen may act on the developing tumor cell itself, during the neoplastic, or developmental, stage, thereby inhibiting or enhancing carcinogenesis.

Carcinogenesis may thus be augmented or inhibited in either the pre-neoplastic or the neoplastic stage. The means, mechanisms, and significance of the changes brought about in these two periods are worthy of differentiation, for such an analysis should result in better understanding. Technics for separating carcinogenesis into stages may not be possible with all types of tumors, but it is certainly practical for the induced skin tumor and probably for the induced sarcoma (1).

That a particular noncarcinogenic procedure may promote or inhibit in one stage of carcinogenesis and not in the other has been shown in the preceding communication (44), which introduces experimental evidence suggesting that caloric restriction definitely inhibits carcinogenesis in the developmental (neoplastic) phase and has little effect, if any, on the initiation (pre-neoplastic) phase. It is even conceivable that a particular substance [3] may have an inhibiting effect in one stage, and a promoting action in the other. The results of Berenblum's experiments with carbon dioxide snow (3, 5) and of Crabtree's with monochloracetone (17) suggest this latter possibility, but it would be premature to say more until this point is carefully tested.

The factual and theoretical considerations discussed in this communication indicate the desirability of testing, when feasible, the effect of a particular agent or procedure (solvent, chemical agent, hormone, physical agent, inflammation, trauma, wound healing, or dietary change) during each stage of carcinogenesis as well as during the whole experimental period. It is likely that such practice will improve our concepts of carcinogenesis and our understanding of the mode of action of the experimental agent or procedure. It may be worth while to repeat that the effects of these agents and procedures may be different for the two stages of carcinogenesis, and entirely unrelated to their effects on the subsequent growth of the tumor.

From comparisons of experimental carcinogenesis in animals and occupational tumors in man it may be assumed that the latent period may be as long as 20 years in the latter. Therefore, from a prophylactic viewpoint, there are practical possibilities of thinking in terms of cocarcinogenic and anticarcinogenic effects on the separate stages of tumor genesis. It would be advantageous to find means and methods that (a) prevent and retard the initiatory stage of carcinogenesis, and (b) retard or do not accelerate its formative stage. On the basis of this discussion, the author believes that these are practical goals.

SUMMARY

Promotion and inhibition of carcinogenesis by means of noncarcinogenic agents and procedures have been described as cocarcinogenesis and anticarcinogenesis respectively. In view of certain experimental data and interpretations from our laboratory, coupled with consideration of the pertinent literature, it appears desirable to emphasize the following:

1. The genesis of a tumor proceeds through at least two stages:

(a) A pre-neoplastic stage (preparation, initiation, inception), which under proper conditions leads to

(b) A neoplastic stage (development, formation).

[3] See footnote 2.

2. Such procedures as wound healing, application of croton resin, and caloric restriction can affect the neoplastic stage, but have little or no effect on the pre-neoplastic stage.

3. Certain solvents and other procedures can have a definite effect during the pre-neoplastic stage, yet may be without significant effect during the neoplastic stage.

4. A particular agent or procedure may have one effect, cocarcinogenic, anticarcinogenic, or none, on the development of the pre-neoplastic stage, and another effect, cocarcinogenic, anticarcinogenic, or none, on the outcome of the neoplastic stage.

5. The desirability of testing, when feasible, the effect of a particular agent or procedure (solvent, chemical, hormone, inflammation, trauma, dietary change) during each stage of carcinogenesis as well as during the whole experimental period.

6. The likelihood that such practice would increase our knowledge of the mechanism of carcinogenesis and have clinical implications.

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The Dependence of the Genesis of Induced Skin Tumors on the Fat Content of the Diet during Different Stages of Carcinogenesis

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The genesis of induced skin tumors is facilitated by a diet rich in fat. Since the results in the preceding reports (7, 8) indicate that carcinogenesis proceeds through two distinguishable phases, (a) an initiatory, or preneoplastic, stage, which under favorable conditions leads to (b) a developmental or neoplastic stage that culminates in the appearance of a tumor, it becomes of interest to ascertain the stage or stages of carcinogenesis in which the facilitating effect of a high-fat diet occurs.

The results of other investigators, who have reported considerable increases in the incidence of induced skin tumors in animals consuming a high-fat diet, have been reviewed (6). In our experiments the increase in formation of skin neoplasms, though real, was of a decidedly lower magnitude. The present communication attempts to explain the reasons for this difference.

The experiments reported in this paper were performed according to the technic described in a previous work (7) on calorie restriction. An arbitrary separation of the phases of initiation and development is achieved by terminating the application of carcinogen just before the first tumor is expected. Under these conditions, the painting period roughly conforms to and contains what may be considered the initiatory phase, while the period following the painting covers the major portion, if not all, of the developmental phase. The effect of a fat-enriched diet on each of the two stages of carcinogenesis is determined by comparing the tumor incidence of mice receiving a high-fat diet during the limited painting period with the tumor incidence of mice receiving the high-fat diet only in the period following the application of the carcinogen.

METHODS

Pure-strain mice, obtained originally from the Roscoe B. Jackson Memorial Laboratory and inbred in our laboratory, were used. Each experimental series was divided into groups of 50 male mice equivalent as to age and weight. Many of the animals in one group of an experiment had litter mates in the other group or groups. The animals were housed 5 to a cage. Each was numbered and a separate record of its progress was kept.

The animals were inspected for tumors and weighed at 2 week intervals; the weights of those bearing carcinomas were not included in the group averages. Papillomas or carcinomas were distinguished by their gross appearance and by palpation; none of the papillomas regressed and eventually many were replaced by carcinomas (7). The tumor count and time of appearance refer to the first perceptible tumor, papilloma or carcinoma, that each mouse developed. Percentages of tumor formation were computed on the basis of the number of animals alive at the time the first tumor appeared in any group of an experiment (effective total) and also on the basis of an adjusted total described by Bryan and Shimkin (1), that accounts for the deaths of nontumor animals during the period in which tumors appear.

At postmorten, the tumors were sectioned and examined in the gross; preparations for histological study were made of many selected at random, and of all lesions about which doubt existed. The results of the histological studies indicate that the gross examinations were reliable.

Two diets were employed. The control diet (low-fat) consisted of 1.4 gm. Purina dog chow meal, 0.9 gm. skimmed-milk powder, and 1.9 gm. cornstarch per day for each animal. The high-fat diet was prepared by substituting 0.9 gm. of hydrogenated cottonseed oil [1] for the 1.9 gm. of starch. Thus, the two diets contained approximately equal quantities of protein, vitamins, and minerals, and differed only in their fat and carbohydrate content. The approximate compositions of the diets in grams per mouse per day were as follows:

	Control (C)		High-fat (F)	
	Gm.	Per cent	Gm.	Per cent
Protein	0.62	15	0.62	19
Fat	0.08	2	0.98	31
Carbohydrate	2.92	70	1.22	38
Ash	0.16	4	0.16	5

[1] The hydrogenated cottonseed oil (Kremit) was generously furnished by Armour and Company.

A week's supply of the weighed dietary constituents was mixed with sufficient water to form an easily molded mash, which was cut into equal blocks, permitted to dry over night, stored in a refrigerator, and fed daily. The actual average food consumption (reported under Results) of each experimental group was ascertained by weighing back each week the food left in the cages. All animals had free access to water.

For convenience the following letter combinations are employed to designate the dietary sequences used in these experiments: CC, control diet throughout the experiment; CF, control diet during the period of carcinogen application, high-fat diet in the succeeding period; FC, high-fat diet during the period of carcinogen application, control diet in the succeeding period; and FF, high-fat diet throughout the experiment.

The results are given in Table I. At the end of the experiment, 49 weeks after the first application of the carcinogen, 18 mice of the S2-FC group had developed tumors, in comparison with 23 in the S3-CF group. A difference of 5 tumors (approximately 10 per cent) corresponds to the degree of augmentation obtained previously by the use of high-fat diets in 5 different experiments (6); the augmentation, though not of large magnitude, occurred consistently and with no exception, and therefore must be considered real. The mean times of appearance of the tumors were 33 ± 2.7 and 28 ± 2.0 weeks respectively. Thus a high-fat diet promotes a higher incidence of benzpyrene skin tumors when fed during the second, or developmental, stage of carcinogenesis than when fed during the initiatory stage (period of carcinogen application).

TABLE I: DEPENDENCE OF THE INCIDENCE OF INDUCED SKIN TUMORS ON WHETHER A HIGH-FAT DIET IS FED DURING OR AFTER A LIMITED PERIOD OF CARCINOGEN APPLICATION

Group	Fat content of diet: During carcinogen application (13 weeks)	Fat content of diet: Following carcinogen application	Number of mice (effective total)	CUMULATIVE TUMOR COUNT: Weeks after first application of carcinogen * 13	17	21	25	29	33	37	41	45	49	Number of mice tumor-free and alive at end of experiment	PER CENT TUMORS: of effective total	of adjusted total
S2-FC	high	low	50	1	2	3	5	7	9	10	12	14	18	28	36	38
S3-CF	low	high	49	0	6	7	10	14	16	18	22	23	23	21	47	50

* Twenty-six semi-weekly applications, terminated before any tumors appeared.

RESULTS

Experiment 1.—Two groups of mice, each consisting of 50 C57 black male mice, born within a span of 3 weeks, were transferred to their respective control and high-fat diets when they averaged 10 weeks of age. After 6 weeks they received the first of 26 semi-weekly applications of 0.3 per cent benzpyrene in benzene. At each application 1 drop of the solution, containing about 0.05 mgm. of the carcinogen, was applied to the skin of the interscapular region by means of a dropping pipette.

No tumors were present at the time of the last application of the carcinogen (13th week after the first application). Two days later the following dietary changes were made: The group (S3) that had been fed the control diet was now transferred to the high-fat diet, while the group (S2) that had been on the high-fat diet was now given the control diet. The groups were designated as S3-CF and S2-FC respectively.

The mice of both groups consumed approximately 3.5 gm. per day when on the control diet and 2.8 gm. when on the high-fat diet. These quantities of food contain approximately the same amounts of essential dietary constituents (protein, vitamins, and minerals); the caloric intake is higher, and the mean weights of the mice 1 to 3 gm. greater, on the fat-enriched diet.

Experiment 2.—In this experiment 4 equivalent groups of 50 male dba mice, 10 weeks of age, were employed. Two of the 4 groups were placed on the control diet, while the other 2 were given the high-fat diet. After 4 weeks the first of 19 semi-weekly applications of a 0.3 per cent solution of 3,4-benzpyrene in benzene was applied to the skin of the interscapular region by means of a dropping pipette.

Two days after the last application of the carcinogen, and before tumors had developed in any of the mice, the following dietary changes were made: One of the groups (S10) being fed the control diet was continued on this ration while the other (S13) was transferred to the high-fat diet; similarly, one of the groups (S11) on the high-fat diet was continued on this ration while the other (S12) was transferred to the control diet. This resulted in 4 groups, which differed with respect to the indicated dietary sequences: S10-CC, S11-FF, S12-FC, and S13-CF. The average daily food consumption of the mice on the control diet was 4.0 gm., and on the high-fat diet 3.1 gm. Caloric intake and body weights follow the same pattern as in Experiment 1. The results are given in Table II. Of the number of mice alive at the time the first tumor appeared in any group (effective total) the percentage of tumors for the four groups are 68, 78, 64, and 82 respectively.

In the same order the mean induction times are 31 ± 1.8, 27 ± 2.2, 31 ± 2.6, and 30 ± 1.9 weeks.

The mice of the S12-FC group (high-fat diet during the period of carcinogen application only) did not develop any more tumors than did the control group (S10-CC), indicating that the high-fat diet had no augmenting effect during the initiatory phase. The other 2 groups, S11-FF (high-fat diet throughout experiment) and S13-CF (high-fat diet during the second period only), exhibited the augmenting effect of fat to approximately the same degree, suggesting that it is the developmental phase of carcinogenesis that is stimulated by the fat-enriched diet.

DISCUSSION

The effects of feeding a high-fat diet during varying periods of the process of carcinogenesis was first reported by Lavik and Baumann (3). They painted groups of mice with a 0.3 per cent solution of methylcholanthrene in dioxan for 2 months. The experimental groups differed only in that they were fed a high-fat diet during arbitrary periods of the experiment. It was found that the high-fat diet was most effective in causing an increase in tumor formation when it was fed throughout the experiment; when fed during only a limited period its effectiveness was of smaller magnitude. The authors conclude that "the highest incidence of tumors appeared when fat was given throughout the experiment, but measurable increases were also observed when fat was fed either during the first 2 months while the carcinogen was applied, or after the second month; *e.g.*, after the application of hydrocarbon had ceased. The most effective [limited][2] period was $1\frac{1}{2}$ to 3 months after the beginning of the application of hydrocarbon."

Our results tend to confirm the work of Lavik and Baumann, since in both investigations the high-fat diets were more effective when fed after the period of carcinogen application than when fed during carcinogen application. However, there are some differences in the results obtained by the two laboratories. In our experiment: (a) feeding the fat-enriched diet only after the application of the carcinogen had been terminated was *as effective* as feeding it throughout the experiment; (b) *no augmenting effect* was obtained when the high-fat diet was fed only during the period of carcinogen application; and (c) the fat-enriched diet fed throughout the experiment did not cause a *large* increase of tumors.

In order to facilitate comparison of the experiments performed by the two laboratories, the results are listed in the following table:

Diet	Percentage of mice (of effective total) that developed tumors by the end of the experiment. Lavik and Baumann	Tannenbaum
Low-fat control.	17	68
High-fat throughout experiment.	86	78
High-fat during application of carcinogen only.	29	64
High-fat after application of carcinogen only.	43	82

TABLE II: STAGE IN WHICH A FAT-ENRICHED DIET IS FED AS A FACTOR IN FACILITATING THE FORMATION OF SKIN TUMORS INDUCED BY A LIMITED PERIOD OF CARCINOGEN APPLICATION

Group	Fat content of diet: During carcinogen application (10 weeks)	Fat content of diet: Following carcinogen application	Number of mice (effective total)	CUMULATIVE TUMOR COUNT: Weeks after first application of carcinogen * 10	14	18	22	26	30	34	38	42	46	50	54	56	Number of mice tumor-free and alive at end of experiment	PER CENT TUMORS: of effective total	of adjusted total
S10-CC	low	low	50	1	2	4	7	9	16	22	27	30	33	33	33	34	3	68	71
S11-FF	high	high	50	4	9	14	18	21	25	28	31	31	36	38	39	39	7	78	79
S12-FC	high	low	50	0	4	8	11	17	20	22	22	24	26	28	30	32	8	64	69
S13-CF	low	high	50	3	6	10	14	16	19	25	33	36	38	40	41	41	7	82	83

* Nineteen semi-weekly applications, terminated before any tumors appeared.

It is probable that these differences are real, and that they are not due to any fundamental error on the part of either laboratory, but to the variables and conditions of the experiments. The most important difference between these two experiments is the degree of oiliness of the skin produced by the contact with a fat-enriched diet; *i.e.*, the fur of Lavik and Baumann's mice was probably oily,[3] while the fur of our mice was not.

It is known (4, 9) that fat applied locally to the skin of mice in the region where the carcinogen is applied increases tumor formation. The mechanism of this effect is as yet unknown, but it may be due to the solvent action of the fat fixing the carcinogen to the painted area, thus permitting less to be lost mechanically (through desquamation, movement, or rubbing) or to easier passage of the carcinogen through the epidermis.

Watson and Mellanby (9), in pioneer experiments, showed that tarred mice maintained on a diet containing a high proportion of butter-fat developed many

[2] Present author's addition.

[3] Inferred from their own statements in reports (2, 4) of other experiments employing similar diets.

more tumors than did controls on a low-fat diet. The coats of the animals on the high-fat diet assumed a characteristic oiliness. Such a high-fat diet produced both an oiliness of the skin and an increase of tumor formation comparable to that seen in groups of animals maintained on the control diet, but whose skins were treated with either mouse fat or olive oil preceding each application of the carcinogenic tar. In a recent publication (4) Lavik and Baumann have also come to the conclusion that much of the effect of the high-fat diets they employed was exerted locally through oiliness of the skin, arising from local contact with the fatty ration.

In contrast, it is important to stress that the coats of the animals in our experiment showed no visible greasiness, even though the fat content of the high-fat diet was higher than in those used by Watson and Mellanby and by Lavik and Baumann. This is probably due to our method of preparing the diet.

The small but consistent increase in tumor formation on a high-fat diet reported by us previously (6) and in this communication, did not occur through the medium of oily skins. Gross examination revealed no significant differences in the skins of the control and fat-fed groups, and examination of sections stained for fat confirmed this impression. It should be emphasized again that the mice of the S12-FC group (fed the high-fat ration during the period of carcinogen application) developed no more tumors than the mice consuming the control diet (S10-CC). This suggests that the increase in tumor incidence in the S11-FF group is not due primarily to an increase of fat on the skin during the period of carcinogen application.

It is likely that the increase in tumor formation in groups S11-FF and S13-CF was due to fat absorbed from the gastrointestinal tract and carried to the skin, where it acted in some unknown way. This effect probably exerts its influence on the transition of the pre-neoplastic to the neoplastic stage.

Thus, fat in high concentration in the diet may have two separate effects: (a) If, through physical contact, it produces an oiliness of the skin in animals that are being subjected to carcinogen application, it facilitates the absorption of the carcinogen and thus produces a considerable increase in tumor formation; (b) the dietary fat is absorbed through the gastrointestinal tract producing systematically a small but definite co-carcinogenic effect on tumor formation. This concept is an example of the general hypothesis stated in an earlier paper (6), dealing with the effects of a high-fat diet on spontaneous mammary tumors, primary lung tumors, and induced skin and subcutaneous tumors. It was stated "that the effects reported may be the resultant of two properties of fat: (a) 'solvent action' on the carcinogen; and (b) 'cocarcinogenic action' on the developing tumor cell."

On the basis of the facts and hypothesis discussed above the differences between our results and those of Lavik and Baumann are to be expected. Since the coats of Lavik and Baumann's mice were oily, the results of these investigators can be explained as the joint effect of both solution of the carcinogen in the greasy skin during the pre-neoplastic stage, and a co-carcinogenic action in the subsequent neoplastic stage. In contrast, our results were obtained with mice whose fur did not become greasy from contact with the diet, and are due only, or mainly, to the cocarcinogenic action of fat in the neoplastic stage; in other words, to nutritional variation and not to a change in oiliness of the coat. It may be helpful to emphasize the necessity of distinguishing between the results that may be obtained under these two conditions.

In addition to giving a better understanding of the effects of fat solvents and high-fat diets on epidermal carcinogenesis, the experiments substantiate the importance of differentiating the stages of carcinogenesis. In a previous publication (7) it was shown that 3 entirely different means, wound healing, croton resin, and caloric restriction, exert a considerable effect on the incidence of neoplasms when applied during the developmental phase, while they exert little or no effect when applied during the initiation phase. To these factors one may now add the augmenting effect of a high-fat diet eaten during the developmental phase of carcinogenesis.

It is probable that at the present time there are not enough facts to explain the promoting effect of a high-fat diet. In both this and an earlier communication we have expressed our general views. Lavik and Baumann (4) have suggested that "much of the systemic or cocarcinogenic activity of dietary fat, if not all, is exerted through the medium of a voluntarily increased intake of calories on diets high in fat." We cannot agree with this conception, since high-fat diets have no effect on the incidence of lung tumors (6); this should be augmented if the effects of such a diet were due to increased caloric intake. In addition, there are data (unpublished) suggesting that tumor formation is accelerated by fat-enriched diets of caloric levels equal to or even less than those of low-fat control diets.

From a practical and clinical viewpoint it becomes important to differentiate between: (a) the results caused by external application of lipids and organic solvents during exposure to carcinogenic agents, and (b) the results of ingestion of a high-fat diet. Fats, oils, and solvents may have a decided augmenting effect on the production of industrial skin cancers or tumors produced elsewhere by agents absorbed through the skin. On the other hand, the ingestion of high-fat diets may produce its augmenting effect independently of oily agents on the skin surface.

In a review of insurance statistics on the relationship

of body weight to cancer (5) it was shown that persons of average weight or less are not so likely to develop the disease as are those who are overweight. If the results on the relationship of nutrition to cancer incidence in mice can be carried over to man it follows that a calorie-restricted and low-fat diet may aid in the prevention of human cancer, or at least delay its onset. Besides, as indicated in this communication, these restrictions should produce beneficial results even if begun after carcinogenic stimuli have been acting for a considerable period of time.

SUMMARY

A fat-enriched diet promotes the production of skin tumors induced by carcinogenic hydrocarbons. Since the carcinogenic process can be divided into two distinguishable stages, initiation and development, it seemed of interest to determine whether the facilitating effect occurs in one or both of these stages. The carcinogen was applied for a limited period only, and the high-fat diet was fed to different groups either during the period of application, in the period following application, or throughout both periods. The ingestion of the high-fat diet during the period following application of the carcinogen exerted a small but definite facilitating influence on the formation of skin tumors, equal to that obtained when the high-fat diet was fed throughout the experiment; no such effect was observed if the high-fat diet was fed only during the limited period of carcinogen application. This suggested that the facilitating effect of the high-fat diet operated principally in the neoplastic or developmental stage of carcinogenesis. In contrast, facilitating effects of greater magnitude have been reported in animals whose skins have become oily from contact with a fat-enriched ration. This effect, due to carcinogen application in the presence of an oily skin, which affects solubility and absorption of the carcinogen, must not be considered a primary effect of a fat-enriched diet. Our high-fat diet was prepared and fed in such a way that the fur of the animals was not oily. Therefore it must be emphasized that one can distinguish between the tumor-promoting effect due to oily skins, in the initiatory stage, and the tumor-promoting effect that is produced systemically by ingested fat, in the developmental phase. The experimental and clinical importance of such differentiation is discussed.

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Influence of Bromobenzene on the Induction of Skin Tumors by 3,4-Benzpyrene*

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It has previously been demonstrated that the rate of tumor induction in mice by chemical carcinogens of the hydrocarbon type is retarded by a series of compounds containing labile halogen atoms (9, 10). These halogen compounds ranged from chloro-acetal, a compound of relatively low reactivity, to a variety of highly active acid halides. The velocity constants of their reaction with cysteine under physiological conditions and their power of checking cell glycolysis followed the same order and ran parallel with their capacities for retarding tumor induction.

The question arose whether the inhibition of the glycolytic process was the effective determinant of the slowing of the carcinogenic process, since, in addition to this action, all the compounds used could affect other cell mechanisms by fixation of sulphydryl groups. This more generalized concept, that disturbances of sulphur metabolism interfere with carcinogenic action, seemed worthy of investigation. For this purpose, substances were required that would affect sulphur metabolism but be devoid of direct, specific action on the glycolytic mechanism. Compounds eliminated as mercapturates should fulfil this role, provided that detoxication occurred locally in the skin. The literature dealing with the elimination of bromobenzene and allied substances describes the liver as the principal site of detoxication, since the toxic substances were normally administered via the stomach. Evidence will be given that bromobenzene can also be detoxicated in the skin and that its application to an area of skin under the influence of a carcinogen effectively retards, and sometimes prevents, the completion of the carcinogenic process.

Since the glycolysis-checking compounds with their active halogen atoms, and bromobenzene with a halogen atom unreactive in the same sense, have the common property of disturbing sulphur metabolism, the inference is made that the latter is the biochemical basis of their anticarcinogenic action.

* Because of the difficulties of international communication the author has not read proof of this article.

EXPERIMENTAL

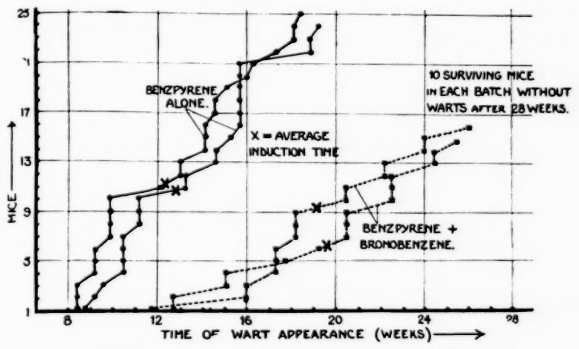
Demonstration of inhibition of carcinogenic process by bromobenzene.—Batches of 30 mice were used in each experiment. The mice were not of pure strain but were all descendants of some 150 hybrids from two breeders' stocks. Their diet was uniform, consisting solely of a mixture compounded and pressed into small bricks and obtained commercially. No details of its composition are given, but its well-balanced nature is reflected in the general good health and normal growth of the mice. From 24 to 28 mice always survived in any treated batch, even if the experiment lasted for 6 to 8 months.

3,4-benzpyrene dissolved in ether containing 2 per cent of liquid paraffin was applied in 0.3, 0.1, or 0.03 per cent concentration twice weekly (Mondays and Thursdays) with a No. 4 brush in the scapular region over an area of approximately 1 sq. cm. Fifteen per cent bromobenzene, by volume, in ether was applied 4 times weekly (Tuesdays, Wednesdays, Fridays, and Saturdays) with a No. 6 brush over the benzpyrene-treated area but widely overlapping it. This amounted to roughly 90 mgm. of bromobenzene per mouse per week. This dose of bromobenzene had no measurable effect on the weight of the mice, and no impairment of health occurred over the longest experimental period.

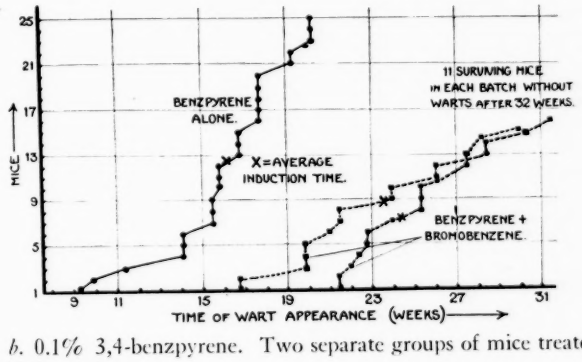
The results are shown in Fig. 1*a, b,* and *c* for benzpyrene concentrations of 0.3, 0.1, and 0.03 per cent respectively. Duplicate experiments were made in some cases and the curves show how closely the average induction times corresponded in such pairs. When the weaker concentrations of benzpyrene were used, almost all the surviving control mice, treated with benzpyrene alone, carried tumors, many of which were epitheliomatous, before a single wart was visible in the bromobenzene-treated mice.

Smaller amounts of bromobenzene caused proportionately less inhibition. To avoid gross systemic effects on the mice due to irreplaceable sulphur losses, larger amounts of bromobenzene were not used. Since it has been shown (3, 12) that benzpyrene or a fluorescent

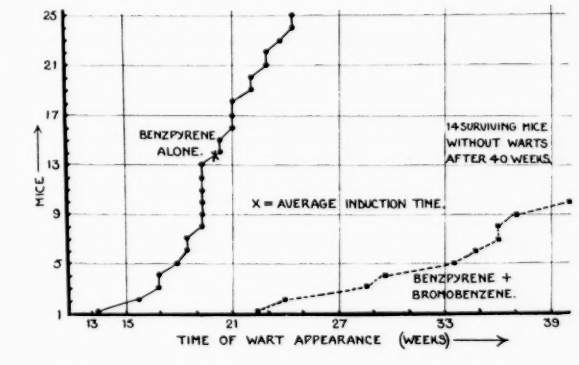
derivative remains at the site of its application for several days, it is conceivable that the observed inhibitory effects of bromobenzene could be attributed to the ether used for its daily application. Dispersal of the carcinogen or its active derivative might occur, the progressive dilution lowering its effective concentration. That this is not the case is readily shown by submitting mice receiving the usual treatment with benzpyrene to daily applications of ether. This procedure causes no significant delay in the rate of tumor incidence.



a. 0.3% 3,4-benzpyrene. Two separate experiments.



b. 0.1% 3,4-benzpyrene. Two separate groups of mice treated with bromobenzene.



c. 0.03% 3,4-benzpyrene.

FIG. 1.—Retarding effect of bromobenzene on the rate of tumor induction by 3,4-benzpyrene applied at different concentrations.

Demonstration that the inhibitory effect of bromobenzene on carcinogenesis is due to its local action.—That the retarding effect of bromobenzene on tumor induction is due to its local rather than systemic action is clearly shown by submitting mice to exactly the same amounts of benzpyrene and bromobenzene, the former applied as usual to the scapular region and the latter to an area of the lower back. In this case, tumors appeared at the normal rate, uninfluenced by whatever deviations from the general level of sulphur distribution the bromobenzene produced. It is clear that local metabolic disturbances in the skin itself are responsible for the biological result, and the presumption is that mercapturate formation takes place in this tissue.

Local sulphur depletion is suggested by another observation. When bromobenzene was applied to the nonepilated skin, it caused a slow, progressive thinning of the hair, tending towards baldness, but under the conditions used never attaining this. This potentiality was masked in the experiments demonstrating anticarcinogenic action, since loss of hair is a characteristic episode in chemical carcinogenesis. In the case of bromobenzene, where the mechanism of detoxication is understood, this effect can reasonably be attributed to a lowering of the level of available sulphur in the hair follicles, which are normally sites of active sulphur metabolism. By analogy, it might be suggested that processes involving sulphur loss are accompaniments in the biological effects of carcinogens. Though naphthalene (6) and anthracene (7) are partially excreted as mercapturates, there is as yet no direct chemical evidence that the carcinogenic or noncarcinogenic hydrocarbons with larger molecules are similarly dealt with, even to a small extent, by the body.

In this connection it may be mentioned that, of the common organic solvents used in the application of carcinogens, benzene tends to delay tumor induction more than, *e.g.,* ether (11). The recent finding of Zbarsky and Young (19) that benzene is partially excreted as a mercapturate may, by analogy with the anticarcinogenic effect of bromobenzene, be an explanation of this hitherto puzzling phenomenon.

Action of Bromobenzene on Precancerous Mouse Skin

The word "precancerous" has no clear connotation in terms of biochemistry. Multiple studies on the metabolism of formed cancer cells and their normal prototypes have demonstrated certain broad differences of enzymic equipment, always of a quantitative type, that accompany, or conceivably cause, the carcinogenic change. But not even the most diffuse picture of metabolic happenings during the "latent period" has emerged. One point, however, seems clear. The early responses of the cell to carcinogens are reversible,

within limits not accurately definable. No evidence is at hand to judge between the alternative conceptions that the carcinogenic change is a sudden event or represents the culmination of a gradual series of changes from normality. In either case, by choosing a point in time prior to the emergence of visible warts and inducing opposing reactions by chemical means, the possibility is opened up of using potential reversibility as the basis of a preventive chemotherapy.

As an extension of the experiments above demonstrating inhibition of tumor induction, the effect of a local depletion of sulphur in a precancerous skin was studied. Several experiments, differing only in the degree of pretreatment with carcinogen, have yielded essentially the same result (Fig. 2). In this case 0.3

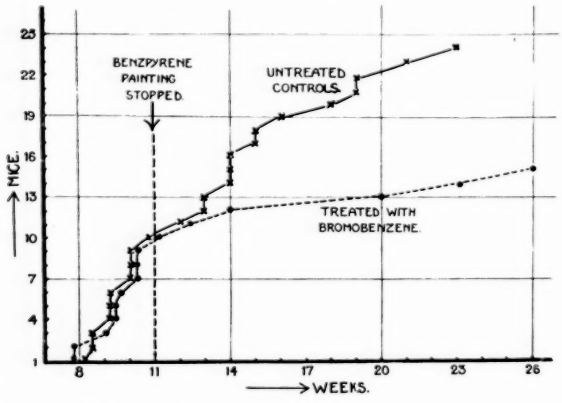


Fig. 2.—Delay and prevention of tumor emergence in a precancerous area of skin treated with bromobenzene.

per cent benzpyrene was applied in the usual way for 11 weeks to two batches of 30 mice each and then discontinued. From this point one group of mice received bromobenzene treatment, the second group serving as controls. Twenty per cent bromobenzene in ether was painted widely over the benzpyrene-treated area of both tumor-bearing and tumor-free mice with a No. 6 brush 4 times weekly. After 26 weeks no further bromobenzene was applied and the mice were examined at intervals. Fig. 2 shows the course of the experiment up to the 26th week. Between the 26th and 39th weeks 3 further warts appeared in the bromobenzene-treated group, but the remaining 9 mice of this group remained free of tumors after a year. Rather a high percentage of mice in both groups carried tumors at the 11th week, and the course of these established tumors was not visibly affected by the bromobenzene. It is clear that the bromobenzene causes a pronounced delay in the later tumor incidence, and in many cases entirely prevents the emergence of tumors. When smaller amounts of benzpyrene were used, say over 6 to 8 weeks, a similar delaying effect was observed, but in these cases the effect was not so obvious since warts only appeared over a very extended time even in the controls.

The conclusion is reached that intermittent interference with the sulphur metabolism of skin in a precancerous condition can delay, and often prevent, the normal course of carcinogenesis. The biochemical basis of this effect is assumed to be the reversibility of reactions involving sulphur that occur in the "latent period."

Effect on Growth Changes and Sulphur Distribution in the Urine of Mice Treated with Bromobenzene via the Skin

In the experiments where 15 per cent bromobenzene was applied 4 times weekly to adult mice no deleterious effect was observed; the records of weight

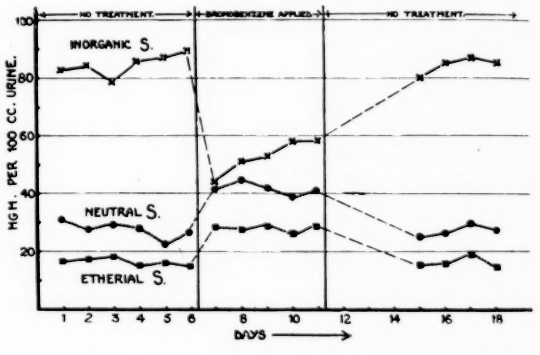


Fig. 3.—Changes of sulphur distribution in the urine of mice treated with bromobenzene via the skin.

changes over several months showed no significant deviation from those of untreated controls. Evidently the organism readily compensates through normal food intake for the temporary sulphur losses produced by this degree of detoxication. But by using younger mice, and applying 50 per cent bromobenzene in ether 4 times a week, growth retardation was readily demonstrated and its correction, by stopping the application of bromobenzene, followed in the usual manner.

Parallel results were obtained in a study of the urinary sulphur distribution. An examination of the urine of mice used in the experiments demonstrating the anticarcinogenic action of bromobenzene failed to show consistent changes that were outside normal fluctuations. When a similar amount of bromobenzene was incorporated in the diet, the same uncertainty of significant changes was found. Again, by increasing the degree of detoxication through the application of 50 per cent bromobenzene, as above, to the skin, notable changes in urinary sulphur distribution, shown graphically in Fig. 3, were obtained. By the method of McGuinn and Sherwin (13) a very small amount of *p*-bromophenylmercapturic acid was isolated from the urine.

Evidently bromobenzene administered via the skin route is excreted by the body in the same way as when given via the stomach. These results, of course, do not prove specifically that the skin is the site of detoxication, though the biological indications suggest this to be the case.

Chemical Evidence that Bromobenzene is Detoxicated in the Skin

Analysis of changes in sulphur distribution in the skin following the application of bromobenzene supports the view that this tissue is not merely a medium for transmission of bromobenzene to the liver, but itself possesses the capacity for detoxication.

Rather than estimate the total sulphur in the skin, which is probably mainly in bound form and not substantially altered by slight applications of bromobenzene, it was decided to use the reservoir of labile sulphur, mainly glutathione, as an indicator of disturbed sulphur metabolism. The literature available provided no data on the normal glutathione content of mouse skin, even though many other tissues have been studied in this respect. All the estimates reported here were made on whole skin, since the technics for separating epithelium used, *e.g.,* by Baumberger, Suntzeff, and Cowdry (2) would adversely affect this labile constituent. Each estimation necessitated the use of 5 to 10 mice to obtain consistent results. For the quantitative determinations mice were epilated over the whole back 2 days before using. The hairless skins were removed after death and quickly minced twice in a fine mincer. The weighed mince was ground with several times its weight of clean silver sand in a mortar, 20 cc. of 10 per cent sulphosalicylic acid solution added, and the mixture reground. After 10 minutes' standing this was filtered at the pump and gave a clear filtrate. The sand-mince was reground with 10 cc. of 10 per cent sulphosalicylic acid solution, allowed to stand for 5 minutes and again filtered. Aliquots of the combined filtrates were titrated against (a) $\frac{N}{1000}$ I_2, (b) $\frac{N}{1000}$ KIO_3, and (c) 0.01 per cent phenol-indo-2,6-dichlorophenol. (a) and (b) should give identical figures representing the sum of the glutathione and ascorbic acid contents, and (c) the ascorbic acid content. The end point when KIO_3 was used was occasionally vague, though Woodward and Fry (18), using it for the estimation of the glutathione content of blood, found a sharp end point. The extract contained no detectable protein, but sometimes was slightly opalescent, and this may have been responsible for the uncertain end point. In the results presented here only the values obtained by iodine titration are given. On the basis of iodine equivalents 1 mgm. of ascorbic acid corresponds to 3.38 mgm. of glutathione, and the glutathione content was obtained by deducting (c) from (a). The averages of many of these determinations on normal skins are shown on the left of Fig. 4. The variations were rarely greater than ±5 per cent when mice of about the same age were used. The values for glutathione and ascorbic acid tended to fall with increasing age of the mice.

The fall in glutathione content after applying bromobenzene to the skin was first shown qualitatively by the use of sodium nitroprusside. To assess the effect of bromobenzene quantitatively, the whole backs of a group of 5 to 10 mice were painted with a suitable dilution 4 times at half-hourly intervals. The glutathione and ascorbic acid estimations were then made at

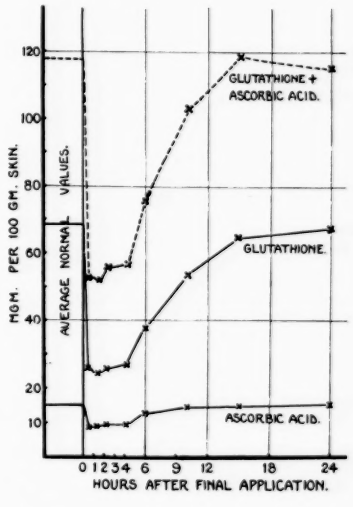


Fig. 4.—Changes in the glutathione and ascorbic acid contents of mouse skin treated with bromobenzene.

varying intervals after the last application. All the data of one typical experiment, in which 20 per cent bromobenzene was used, are gathered in Fig. 4.

In this experiment the amount of bromobenzene applied was 5 to 6 times greater than the daily application in the experiments demonstrating inhibition of carcinogenesis. Under the latter conditions a milder and possibly less prolonged disturbance of sulphur metabolism may be inferred.

The principal features that emerge from these findings are: (a) The high speed of detoxication in the skin, and the relatively rapid recovery to a normal level. (b) The concomitant fall in the ascorbic acid content of the skin that occurs with the reduction of the glutathione level, and the parallel rates of their recoveries to normal values. It may be added that successive applications of ether to the skins of mice in amounts greatly exceeding those used for applying the bromobenzene produced no detectable changes

in the concentration levels of glutathione and ascorbic acid.

Observations on these results.—The experimental conditions were chosen arbitrarily mainly with a view to avoiding general systemic deterioration in the mice from excessive sulphur losses. The doses of bromobenzene applied were readily tolerated and general health and normal growth were maintained. The measurements of the fall and subsequent rise in the skin glutathione levels reveal the fact that this degree of treatment produces only slight local intermittent disturbances of sulphur metabolism. Yet these occasional falls in the level of the reservoir of labile sulphur are adequate to cause considerable delays in the carcinogenic action of benzpyrene, and in some cases to annul it. It is conceivable that the recovery to normal glutathione concentration is not a true index of a complete return to normal sulphur metabolism, and that the disturbances in enzymic systems dependent on sulphydryl groups for their proper functioning persist much longer than this indicator suggests. Until this is proved it must be assumed that well-spaced fluctuations in local sulphur metabolism are responsible for the biological results.

These conditions may be contrasted with the continuity of sulphur imbalance that prevails during typical experiments on the relation of diet to cancer. Examples of the effects on carcinogenesis of such prolonged impairment of normal metabolism are found in the work of Tannenbaum (14) and White and Andervont (15). In the latter case the occurrence of spontaneous mammary gland tumors in the females of a strain of mice with a customary incidence of 100 per cent was entirely prevented by a diet relatively low in its content of S-containing amino-acids. Extreme growth failure and disturbed ovarian hormonal function were the accompaniments of the failure in tumor occurrence, making interpretation difficult. A less drastic dietary regimen, perhaps with S-deficient diets alternating with complete diets, might permit a differentiation between any primary effect of S-deficiency on spontaneous carcinogenesis and such secondary effects as may arise from disturbed hormonal function.

Conversely, as an extension of the experiments with bromobenzene, it is interesting to speculate on the effect of enhancing local sulphur deficiency either by intermittent use of more potent inhibitors or, preferably, by promoting greater continuity of slighter disturbances, with the object of entirely opposing carcinogenic action.

Little is known of the biochemical mechanisms involved in the action of chemical carcinogens. Many studies (4, 5, 8, 12) have shown that a large but uncertain percentage of carcinogenic hydrocarbons administered intravenously or intraperitoneally are eliminated as oxidized derivatives. These oxidation products exhibit little carcinogenic activity (4) and are normally regarded as end products of detoxication processes. Whether they have any role in the process of cancer induction is unknown. Running parallel with this work on the transformation and elimination of carcinogens, the work of White and White (16) has shown that certain of these agents fed in appropriate doses to young rats cause growth failure analogous to that induced by many substances known to be removed as mercapturates. Unless the assumption is made that the oxidation products cause growth inhibition prior to their elimination, the natural conclusion is that the carcinogens are partially detoxicated by mechanisms involving the S-containing amino-acids, though no mercapturate or other S-containing end products have, as yet, been detected.

Interference with sulphur metabolism may, on the basis of the work of White and White, also account for the findings of Badger, Elson, Haddow, Hewett, and Robinson (1), who showed that the intraperitoneal administration of colloidal carcinogens, and some chemically related noncarcinogenic compounds, definitely inhibited the growth of transplanted, chemically induced, and spontaneous tumors. This growth inhibition did not appear to be specific for tumors, since general body growth was also retarded.

All the work mentioned above is concerned with mechanisms of elimination of carcinogens, and the biological effects can be visualized as secondary to sulphur deprivation, though precise proof is lacking. The part played by sulphur in the carcinogenic process, if any, still remains an open question.

In an attempt to understand the effect of inhibitors of sulphur metabolism on cancer induction, two points of view may be considered:

1. The association of growth with sulphur metabolism is well established. On this basis it could be assumed that local S-depletion lowers the potentiality for normal growth and this, in turn, delays or prevents the incidence of abnormal growth; *i.e.,* that the carcinogenic change can occur only in growing cells. As an extension of this, if it be supposed that the carcinogenic change is unaffected by S-depletion and occurs within normal time limits, then the apparent inhibition could be attributed to the delay in the rate of growth of malignant cells. This conception of the action of inhibitors of sulphur metabolism would certainly account for the delayed tumor emergence shown in Fig. 1. It implies that they are entirely unspecific and that they could well be replaced by any substances that depress the level of any of the chemical factors indispensable for cellular growth.

2. A consideration of the results shown in Fig. 2 suggests that this conception is inadequate. The distinc-

tion between growth, whether normal or malignant, and the processes culminating in carcinogenic change must be emphasized. When the application of a carcinogen to a precancerous tissue is stopped, tumors continue to appear without further stimulus in numbers determined by the intensity of the pretreatment. The inference is that the limited treatment has either already induced the carcinogenic change or that the metabolic conditions prevail that inevitably lead to this event. In either case the action of an inhibitor of sulphur metabolism that solely interfered with growth could only retard the emergence of visible warts, and its removal should permit their normal development. In the experiment shown in Fig. 2 this occurred in a few cases, but the majority of the mice remained tumor-free for 6 months after the bromobenzene treatment was discontinued and growth was therefore not impeded. To account for such results the concept of reversibility must be introduced, a reversibility made possible by occasional interferences with sulphur metabolism. This result would be anticipated on the hypothesis that the carcinogen acts primarily by forming a dissociable complex with cell constituents through sulphur linkages. Wood and Fieser (17), on the basis of considerations of the chemical reactivity of the carcinogenic hydrocarbons, suggested such a coupling as a possible first stage in their biological action.

SUMMARY AND CONCLUSIONS

The carcinogenic action of 3,4-benzpyrene on mouse skin is inhibited, and sometimes prevented, by local applications of bromobenzene to the skin 4 times weekly.

In a precancerous area of skin, bromobenzene greatly delays, and often prevents, the emergence of visible tumors.

The influence of bromobenzene is local and evidence is given that it is due to intermittent interference with sulphur metabolism. Glutathione and ascorbic acid levels in the skin are lowered quickly after bromobenzene treatment, but recover to normal values after a few hours. All the chemical and biological evidence supports the view that bromobenzene is detoxicated by mercapturate formation in the skin before being excreted in the urine.

The possible relation of sulphur metabolism to carcinogenesis is discussed.

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The Influence of Malignant Cells upon the Growth of Fibroblasts *in Vitro**

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Previous Work on the Interaction of Normal and Malignant Tissues *in Vitro*

The stroma reaction induced by the transplantation of carcinoma cells indicates that they stimulate the growth of connective tissue cells *in vivo.* Interaction between the two kinds of cells in tissue cultures has been most extensively studied by Fischer and his collaborators (2, 3). They have demonstrated that the growth of carcinoma is stimulated by contact with fibroblasts, and that the growth stimulus decreases in inverse proportion to the time elapsing since contact was established between the two tissues. The stimulation is said to occur in two stages. First, at the approach of the carcinoma to the normal cells, and second, during their infiltration. The first stimulation is assumed to be induced by relatively stable substances occurring in the immediate vicinity of the fibroblasts, while the second is attributed to "desmones," substances that are unstable extracellularly and can be transmitted only by direct contact between cells. The figures and graphs published by Fischer and his collaborators show that the growth of the Ehrlich mouse adenocarcinoma was increased approximately four times after contact with fibroblasts.

No quantitative data were published concerning the stimulation of fibroblastic growth by carcinomas. Fischer (3) remarked that normal mouse tissues grew rather badly, under the conditions employed, in a mixture of rat and fowl plasma. "On the contrary it is a fact, constantly observed, that the same normal mouse tissue cells proliferate vigorously as soon as they are grown with a carcinoma and come in contact with it." Then, after the two have grown together for a time, the proliferative power of the normal cells declines and finally they are no longer distinguishable amongst the carcinoma cells. Fischer adds that one also notices in cultures in which the growth zones of the carcinoma and fibroblasts have not yet come in contact, when the distance between the two cultures is relatively small, that the connective tissue cells lying nearest to the carcinoma cells degenerate and disintegrate earlier than those on the distal side of the culture. This, he says, indicates that the carcinoma culture gives off metabolic products that are directly injurious to the normal connective tissue cells. He considers this process to be comparable with what occurs *in vivo,* when carcinoma cells are transplanted; the latter stimulate the stroma reaction, but also bring about the destruction of the stromal cells.

Interaction between normal cells *in vitro* was investigated by growing together chick iris epithelium and chick fibroblasts. Neither tissue influenced the growth of the other, but when cultures of the two types of cells grew in contact the area attained by both was less by 25 to 30 per cent than the controls, owing to reciprocal mechanical obstruction, since neither tissue infiltrated the other.

When the Crocker rat sarcoma 10 was explanted with fibroblasts the growth of the latter was retarded to approximately the same extent, but the reduced size of the fibroblast cultures was attributed to infiltration and replacement of fibroblasts by sarcoma cells.

Our experiments have been carried out with different tumors and by different technics, and have led us to other conclusions. It will therefore be desirable to consider briefly in what respects our experimental procedures differed.

Technic of Previous and Present Researches

Fischer and his collaborators worked with flask cultures (Carrel's type D, 3.5 cm. in diameter). A typical experiment will serve to illustrate the difference between his and our methods. For the purpose of investigating the interaction of fibroblasts and carcinoma he explanted the tissues on a coagulum composed of equal parts of rat and fowl plasma, diluted with 66 per cent Tyrode solution. On one side of the flask a fragment of carcinoma and another of connective tissue were explanted so close together that the outgrowths would come in contact. Two similar fragments, serving as controls, were explanted on the other side of the flask, but so far apart that no contact

* Because of the difficulties of international communication the authors have not read proof of this article.

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would be established between them. The cultures were supplied with a nutrient medium consisting of 50 per cent rat serum in Tyrode solution. Growth was measured daily with a planimeter. Although the cultural conditions were satisfactory, it seems to us that diffusion of any growth substances in the fluid phase would tend to affect the control culture although possibly to a lesser extent. To obviate this objection we have worked mostly with large coverslip cultures, but have also extended our observations to flask cultures. The present paper concerns only one aspect of the problem; namely, the influence of normal and malignant cells on the growth of fibroblasts.

Most of our experiments have been carried out as follows:—

A fragment of connective tissue has been explanted equidistant between 2 fragments of malignant tissue, so that the explants were approximately 2 mm. apart. The controls consisted of similarly arranged cultures of 3 fragments of the same connective tissue. Various mixtures of fowl and rat plasma have been employed, usually 3 parts of rat plasma to 2 parts of fowl plasma, with the addition of an equal volume of weak rat embryo or spleen extract (10 per cent). Within 24 hours of explantation, the area of the middle explant was measured with a squared eye piece. For each experiment we had 6 to 10 control cultures (fibroblasts only) and an equal number of mixed cultures (fibroblasts growing between malignant cells). On each occasion that measurements were made, growth indices were calculated as follows:—

$$\frac{\text{Total area of culture} - \text{area of original explant}}{\text{Area of original explant}}$$

Our growth index therefore indicates the number of times the area of outgrowth exceeds the original area of the explant.

To anticipate the results of the experiments to be described, we would point out that our findings differ from those previously reported since we adduce evidence that mammary carcinomas, particularly those of high-cancer-strain mice, liberate some agent that is a powerful stimulant of fibroblastic growth. Sarcoma cultures, however, inhibit the growth of fibroblasts without coming in contact with them.

Protocol of an Experiment Demonstrating the Growth Stimulation of Fibroblasts

To avoid repetition a summarized protocol of a typical experiment is given, followed by a general review of our results.

1. *Tissue cultivated.*—(a) Fibroblasts from hearts of 1 day old mice of the C57 low-cancer strain. The control cultures consisted of 3 explants, the growth of the middle one being measured. Similar explants were grown between 2 fragments of each of the following tissues:—(b) A mammary carcinoma of the high cancer strain, Strong A. This tumor had been transplanted in mice of the same inbred strain for 4 generations. The general growth characteristics *in vitro* of similar tumors have been described by Lewis and Strong (4). (c) The transplantable mammary carcinoma 63 of this Laboratory. The tumor employed was from a strain that had been transplanted for 355 generations. Its behavior in tissue cultures has been reported by Ludford (5). (d) Kidney tissue from embryo RIII mice (high-mammary-cancer strain). This tissue was selected as an example of nonmalignant epithelium, since we had no pure strain of epithelial cells in cultivation. It would have been preferable to use mammary gland epithelium for this purpose, but we have not succeeded in maintaining a strain of such cells in continuous cultivation, and the growth of primary cultures varies considerably. Embryonic kidney tissue was therefore used as it invariably forms sheets of epithelium, but such cultures are far from satisfactory since they also contain varying numbers of fibroblasts.

2. *Culture medium.*—All tissues were explanted in a mixture of 3 parts of rat plasma to 2 parts of fowl plasma, with the addition of an equal volume of rat spleen extract (10 per cent).

3. *Growth characteristics of the tissues employed.*—(a) Fibroblasts. None of the fibroblast cultures liquefied the clotted plasma culture medium, either in the controls or experimental series. (b) Strong A mammary carcinoma. All explants were surrounded by liquefied areas on the second day and the cultures exhibited extensive liquefaction after 4 days. There was some spreading out of carcinoma cells on the surface of the cover slip in liquefied areas. (c) Transplantable carcinoma 63. None of the explants liquefied the plasma until the third day, but all had done so to varying degrees by the eighth day. (d) Embryo kidney. Sheet growths of epithelial cells were apparent in half of the cultures after 2 days; these ultimately tended to disintegrate as the result of liquefaction of the plasma. There was considerable fibroblastic growth, and old cultures consisted of a central mass of kidney epithelium surrounded by a peripheral growth of fibroblasts extending out into the medium.

(4) *Measurement of growth of fibroblasts.*—Fibroblastic growth was measured in 6 cultures of each group in the manner previously described. Areas of outgrowth were measured on the second, fourth, sixth, eighth, and 11th days. The average growth index for each type of culture was calculated on these days.

The results are shown graphically in Fig. 1, where each of the curves represents the average growth indices of 6 cultures.

Results of Experiment

Fig. 1 demonstrates that fibroblasts, in the presence of the Strong A carcinoma, grow more rapidly and the cultures attain a considerably greater size than when fibroblast cultures are grown together. Furthermore, that the growth of fibroblasts is also stimulated

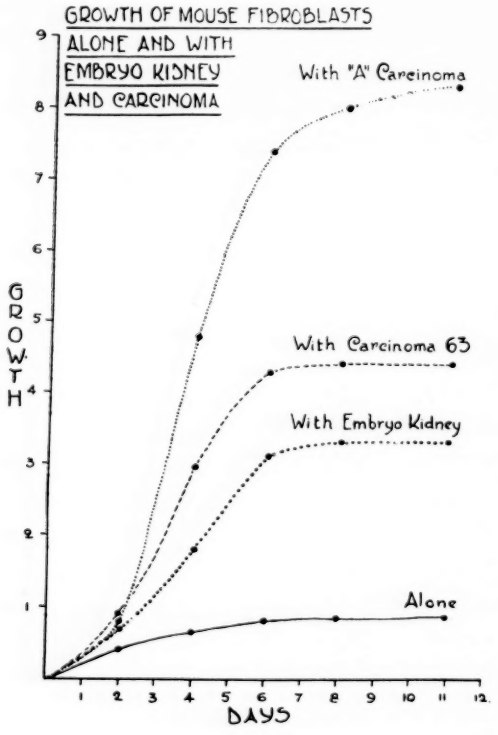

Fig. 1

by the presence of embryo kidney and by the transplantable carcinoma 63.

The extent to which fibroblastic growth is stimulated by a Strong A carcinoma is further illustrated by Figs. 2 and 3, which were photographed at the same magnification from cultures of another experiment. Fig. 2 shows the greatest growth attained by a control culture after 9 days, while Fig. 3 is part of the best culture that grew between 2 explants of another Strong A carcinoma. In control cultures the cells tend to spread out more, and especially around the periphery they are flattened out on the surface of the glass, but in cultures like that of Fig. 3 the cells are usually more spindle-shaped and marginally are often arranged in whorls.

Cell division persists much longer in the latter type of culture, as is illustrated in Fig. 4, which represents a small area of the periphery of the same culture proximal to the carcinoma. There are to be seen, passing from left to right, an early telophase, a metaphase, and a late telophase. Control cultures of the same age exhibited no mitoses.

General Review of Results

Experiments similar to that described have been carried out with a variety of different tumors and with connective tissue from different sources. A comparable degree of stimulation of fibroblastic growth has been induced by mammary carcinomas from the following strains of mice:—

I. High-mammary-cancer strains
- Strong A — 5 different tumors
- RIII — 4 different tumors
- C3H — 1 tumor

II. Medium-mammary-cancer strain
- Bagg albino — 1 tumor

Also, we have obtained similar results with 2 tumors induced in a hybrid mouse (S low-cancer strain mother × RIII father) by the injection of dried RIII tumor. All these tumors are alike, therefore, in that the "mammary tumor inciter," or milk factor of Bittner (1), was concerned in their etiology. The fibroblastic growth-stimulating property is common to both primary and transplanted carcinomas of this type.

All types of mouse fibroblasts with which we have worked respond similarly to these tumors. Thus this property is exhibited by:—

I. Embryonic and adult fibroblasts
II. Fibroblasts from heart, kidney, mammary gland, dermis, and limb bud
III. Fibroblasts from both high-cancer and low-cancer strains, and also from hybrids

Our technic has revealed no significant differences in fibroblastic growth, whether the tumors are of the same or of different genetic constitution.

In most of our experiments the average maximum growth index of fibroblasts grown in the presence of mammary tumors of the high-cancer strains Strong A, C3H, and RIII has amounted to 8 to 10 times that of controls. Occasionally growth of the control cultures has been very limited. Reference has already been made to Fischer's similar experience when growing mouse fibroblasts alone. With one of our experiments, when this occurred the average maximum growth of the fibroblasts in the presence of a Strong A carcinoma was 35 times that of the controls.

All the experiments described have been carried out with primary cultures that had received no further treatment subsequent to explantation. Occasionally the fibroblastic growth impinged upon the outgrowth of carcinoma cells. In such cases there was no in-

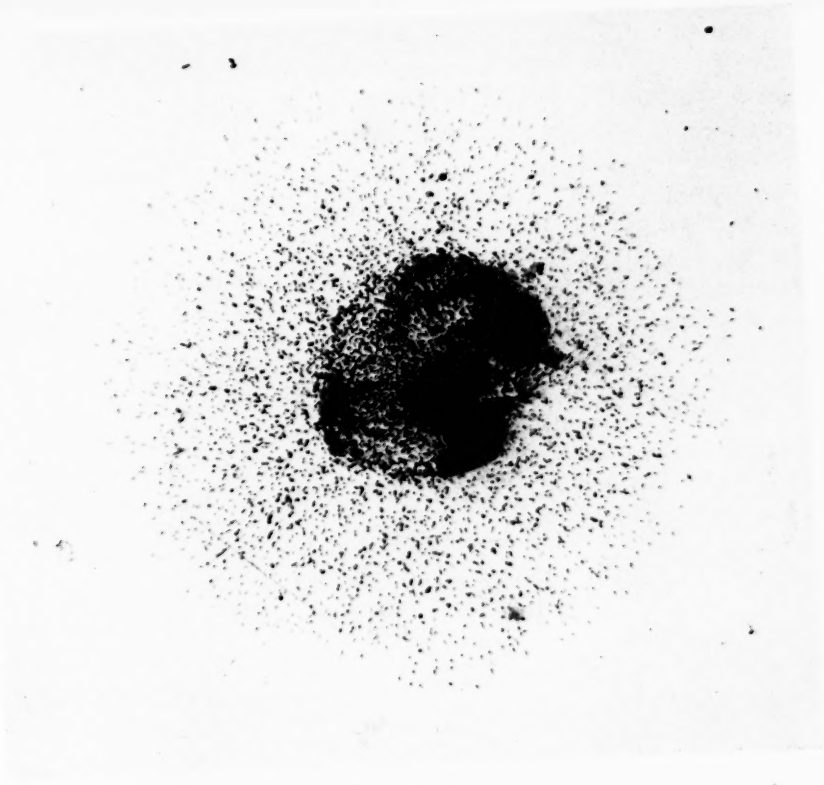

FIG. 2

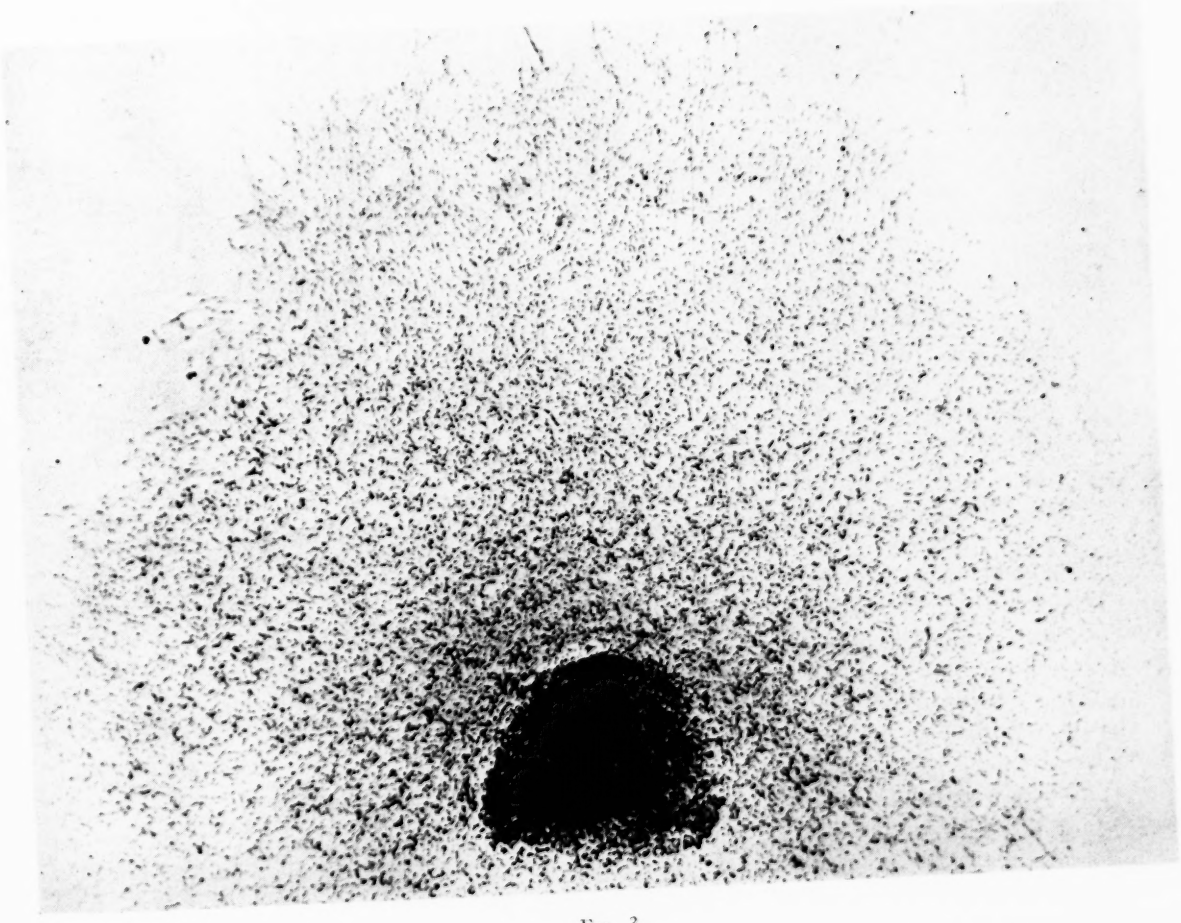

FIG. 3

FIGS. 2 and 3.—Growth of fibroblasts from explants of 1 day old mouse hearts. Nine day old cultures.

FIG. 2.—Control culture grown between 2 similar cultures of embryo heart.

FIG. 3.—Part of a culture of the same tissue, at the same magnification, grown between 2 explants of a Strong A mammary carcinoma.

dication that the fibroblasts were injured. The normal and malignant cells remained in contact, and small papillae of carcinoma cells penetrated into the compact fibroblastic growth. Their subsequent development could not be followed in these primary cultures, which did not survive long enough. Flask cultures were therefore prepared by the same technic as previously described (6). Approximately the same number of fragments of carcinoma and embryonic subcutaneous connective tissue were explanted, each flask receiving 6 to 8 explants. The fluid phase, or nutrient medium, consisted of rat embryo extract (5 per cent) in Tyrode solution. The carcinoma explants liquefied the coagulum of mixed fowl and rat plasma within a few days, and it had to be restored by the addition of fresh plasma. The cultures were washed and re-fed with fresh tissue extract at intervals of 3 to 6 days. Growth of fibroblasts was most prolific, and when the coagulum was liquefied they grew on the surface of the glass. In none of the flasks did the carcinomatous growth dominate the fibroblastic, which was always luxuriant. This result indicated that when the waste products of metabolism are not allowed to accumulate the growth of fibroblasts is not suppressed by the tumors with which these experiments have been performed. Nevertheless, that an injurious action can also be induced by malignant growth has been demonstrated by planting fragments of mammary carcinoma on top of cultures of connective tissue, in cover-slip cultures. Under these conditions the carcinoma grows over the fibroblasts, and those uncovered around the periphery degenerate after a few days. It would appear that certain metabolic products of carcinoma cells are definitely injurious to fibroblasts, but that the growth-stimulating agent is more potent when the former are not present in excess.

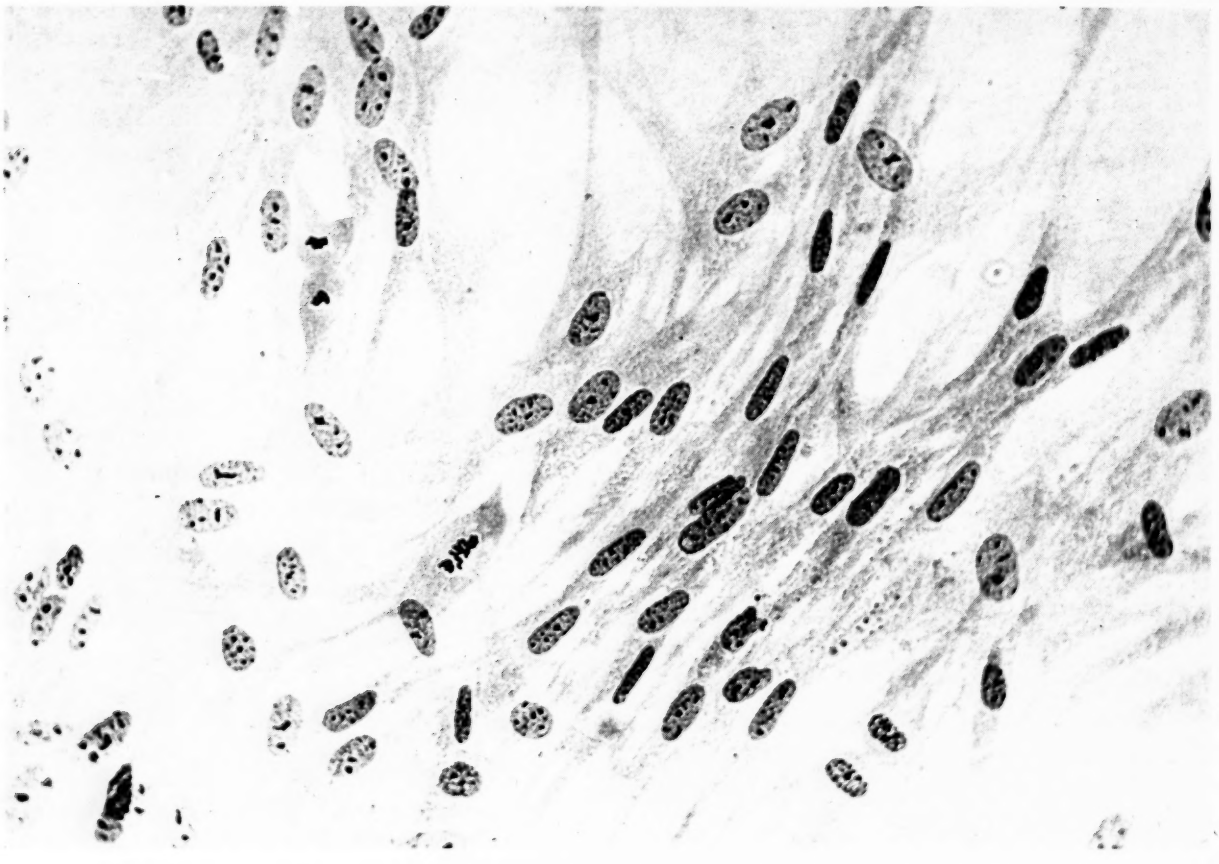

FIG. 4.—Fibroblasts at periphery of same 9 day old culture of mouse embryo heart as Fig. 3. These cells were growing towards the nearest carcinoma culture. Three phases of cell division are represented.

That the stimulation of fibroblastic growth by carcinomas occurs irrespective of the nature of the culture medium was demonstrated by employing a completely heterologous medium for explantation. Fragments of mouse embryo heart were grown as the source of fibroblasts, and the carcinoma was obtained from a mouse of the Bagg albino strain. Coverglass cultures were prepared of embryo tissue alone and with carcinoma in 2 different media: (a) a mixture of equal quantities of rat tissue extract and rat plasma, and (b) a mixture of equal quantities of fowl tissue extract and fowl plasma. Growth in the

rat medium attained nearly 10 times that in the fowl medium, but the relative stimulation of fibroblastic growth by the carcinoma was approximately the same in both media, namely 4 times. These results are shown graphically in Fig. 5.

Reference has already been made to the difficulty of obtaining good cultures of normal mammary gland. It seemed worth while trying whether mammary gland tissue could be stimulated to grow better in the presence of a mammary carcinoma. Fragments of

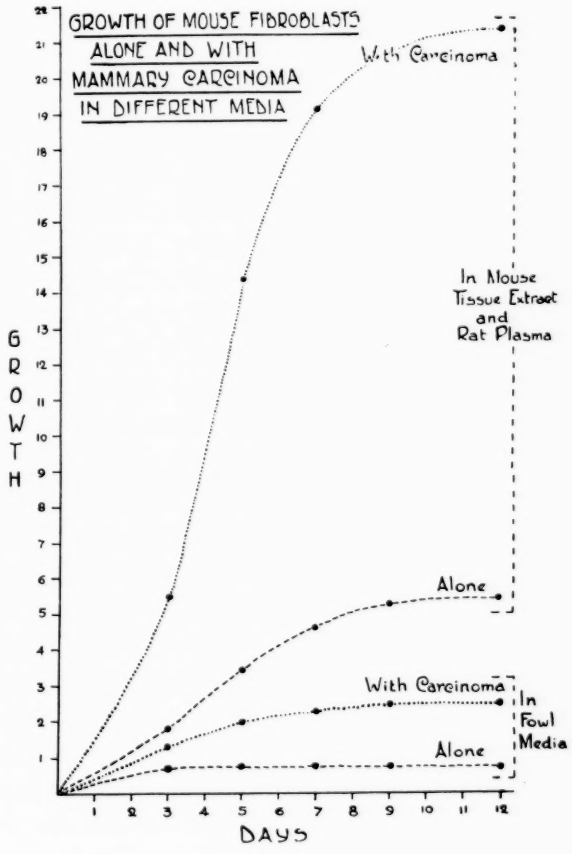

FIG. 5

mammary gland of a mouse in an early stage of pregnancy were therefore grown alone, and also between 2 explants of a mammary carcinoma of the Bagg albino strain. However, it was the fibroblasts of the connective tissue framework of the gland that were stimulated, and not the glandular epithelium. The extent of the growth stimulation is illustrated in Figs. 6 and 7. The former represents the largest growth of fibroblasts amongst the controls, and the latter the best growth in the presence of the mammary carcinoma.

Finally, this investigation was extended to include the action of sarcomatous growth upon fibroblasts. The sarcomas employed had been induced in inbred strains by the subcutaneous injection of methylcholanthrene. We are indebted to our colleague, Dr. L. Dmochowski, for these tumors. The sources of the fibroblasts and the sarcomas used for three experiments were as follows:—

Experiment 1.—Fibroblasts from hearts of 1 day old C57 mice. Transplanted sarcoma of C57 mouse.

Experiment 2.—Fibroblasts from hearts of 1 day old mixed hybrid mice. Primary sarcoma of Strong A mouse.

Experiment 3.—Fibroblasts from hearts of S strain embryos. Primary sarcoma of S strain mouse.

In each of these experiments the maximum growth attained by fibroblasts grown between cultures of sarcomas was less than that of the controls. The ratio, experimental/controls, varied from 0.8 to 0.9. The reduced size of the fibroblast cultures was not the result of infiltration by sarcoma cells, as in Fischer's experiments, since in our cultures the outgrowths from the sarcoma explants did not quite reach the margin of the fibroblastic growths. Neither could the inhibition be attributable to the liquefaction of the plasma medium, which is such a characteristic feature of sarcoma cultures, for some of the mammary carcinomas that stimulated fibroblastic growth to the greatest extent liquefied the medium extensively. Prolific fibroblastic growth has occurred between 2 cultures of carcinoma that have consisted of little more than rounded explants, surrounded by pools of liquefied plasma.

The difference between the action of a Strong A carcinoma and an S sarcoma upon the same embryonic tissue is demonstrated by Fig. 8. This depicts tracings of 2 cultures of another type, in which single fragments of each tumor were explanted with 2 fragments of embryonic tissue. The 2 cultures illustrated were those with the best growths of fibroblasts in each series after 6 days' growth *in vitro*. Although the growth of fibroblasts in the presence of the carcinoma is not so extensive as in the cultures previously described, yet it is considerably greater than in the presence of the sarcoma. That in the same type of culture fibroblastic growth is actually inhibited by the sarcoma is further demonstrated by Fig. 9, which depicts tracings of 3 other 6 day old cultures; Fig. 9A represents the best growth of the same S sarcoma, Fig. 9B the most extensive growth of fibroblasts from an S embryo in the presence of the sarcoma, and Fig. 9C the greatest growth of fibroblasts from S embryo heart alone. It will be observed that the inhibition of fibroblastic growth in Fig. 9B is correlated with a more extensive growth of the single sarcoma explant.

DISCUSSION

The experiments that have been described represent the first part of a research on the biological character-

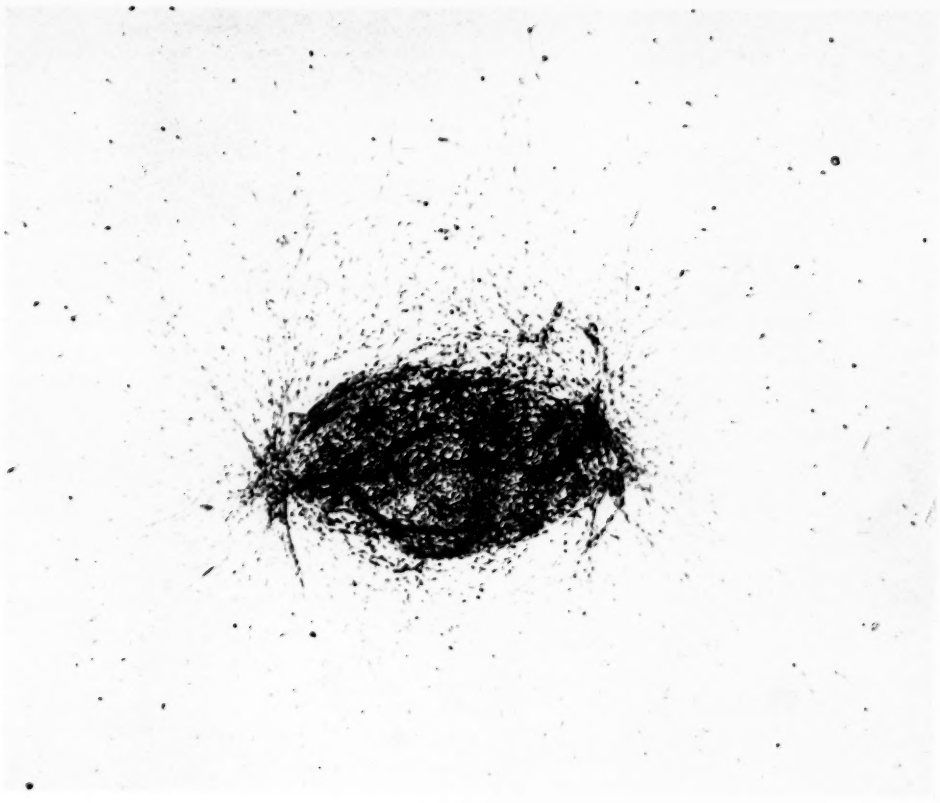

FIG. 6

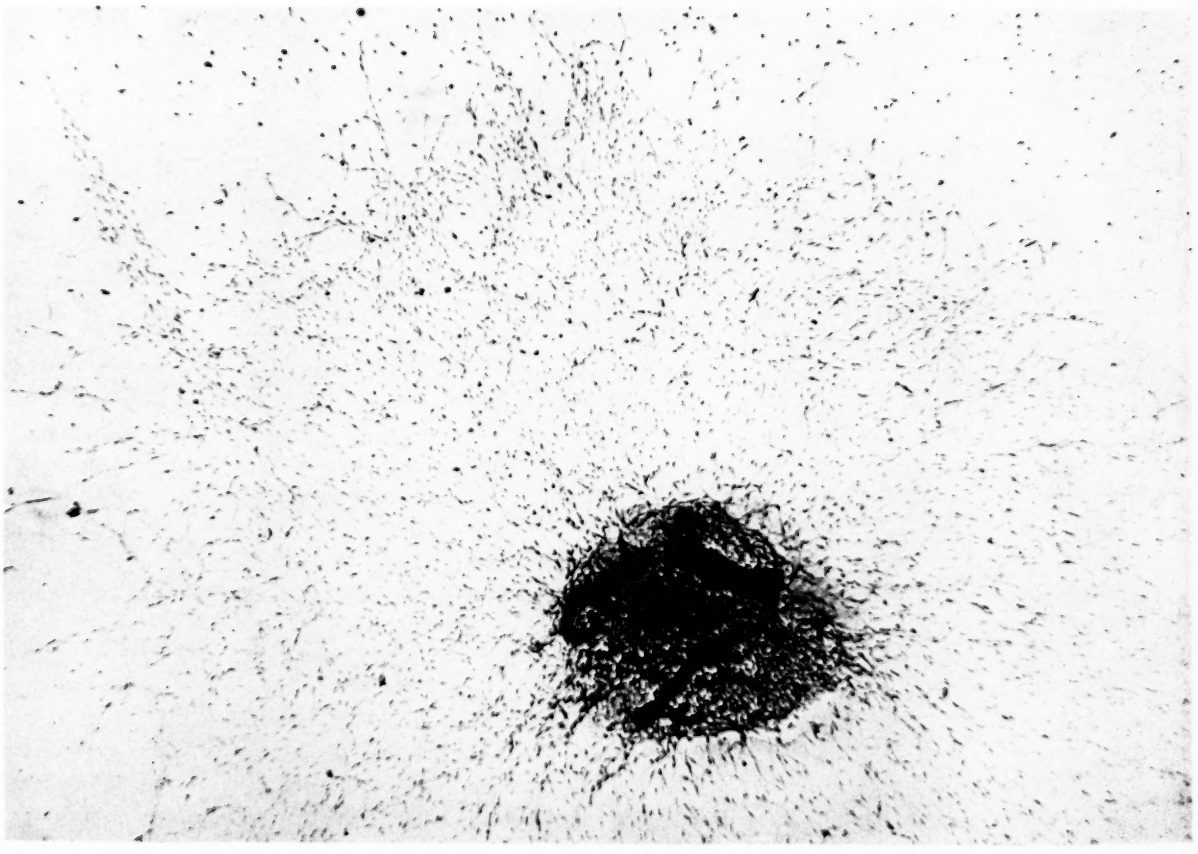

FIG. 7

FIGS. 6 and 7.—Growth of fibroblasts from explants of mouse mammary gland. Six day old cultures.
FIG. 6.—Control culture grown between 2 similar cultures of mammary gland.
FIG. 7.—Part of culture of the same tissue, at the same magnification, grown between 2 cultures of a Bagg mammary carcinoma.

istics of tumors of inbred strains of mice. We have adduced evidence that mammary carcinomas of high-cancer strains have a pronounced stimulating action upon fibroblastic growth, while sarcomas induced in either high-cancer or low-cancer strains by a carcinogenic hydrocarbon have a growth inhibitory action. It will be recalled that both embryonic kidney and the transplantable carcinoma 63 also stimulated the growth of fibroblasts, but to a less extent than tumors of high-mammary-cancer strains (Fig. 1). There is the possibility that some product of the metabolism of growing epithelial cells may stimulate fibroblastic growth. By such means epithelial cells growing in the tures of the latter tumor exhibit innumerable mitoses, unlike those of the Strong A tumor, which, however, was characterized by the greater facility with which its cells spread out in sheet formations. The cytoplasm of the cells of carcinoma 63 stains more intensely basophil (deep red with pyronine), and their nuclei contain relatively more chromatin demonstrable by the Feulgen technic. They may therefore be presumed to be richer in both oxy- and desoxyribose nucleotides. Nevertheless, they exert less growth stimulation upon fibroblasts than cells with less nucleoproteins and a slower rate of growth—a rather contradictory result in view of the evidence that has been

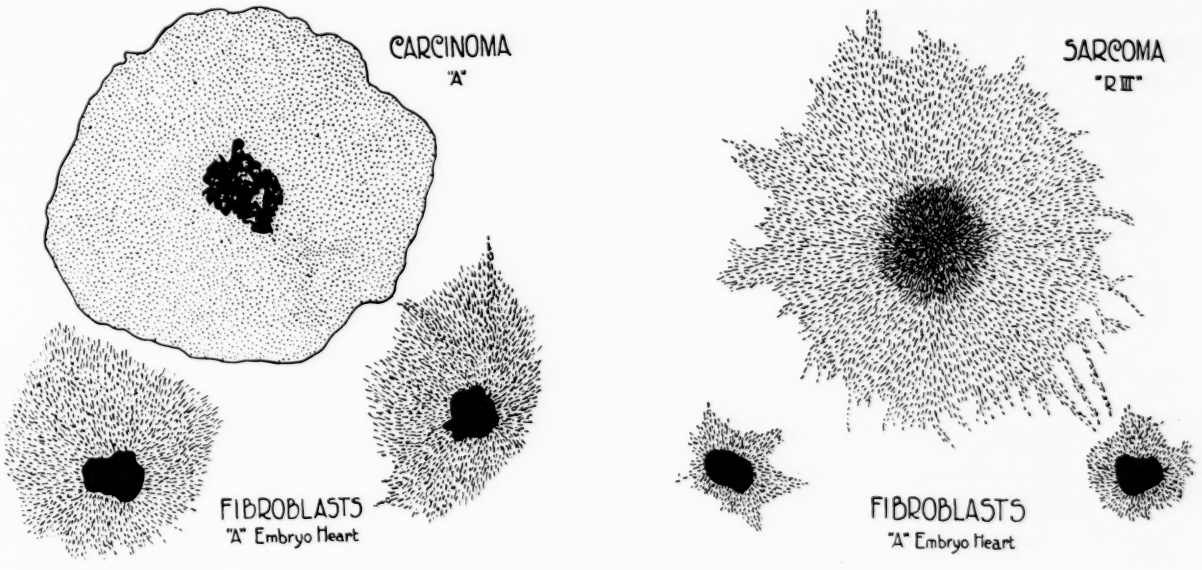

FIG. 8.—Semidiagrammatic tracings of 2 cultures after 6 days' growth, demonstrating difference in growth of fibroblasts in presence of: (a) a mammary carcinoma from a Strong A mouse, and (b) a sarcoma from an RIII mouse.

body might ensure an efficient connective tissue framework for their support. This aspect of the problem requires further investigation, before one can assess the extent to which it can explain the considerable growth-stimulating action of mammary carcinomas from the high-cancer strains.

While this investigation was in progress there have been grown between 2,000 and 3,000 cultures of fibroblasts with the transplantable carcinoma 63 for other purposes. That fibroblastic growth in such cultures is stimulated has been repeatedly confirmed, but the growth stimulation has not on any occasion attained that exerted by tumors of the high-cancer strains. Obviously growth stimulation is not directly proportional to the rate of tumor growth. Grafts of a Strong A carcinoma, with which several of our experiments were conducted, took on an average from 3 weeks to a month to reach the same size *in vivo* as grafts of carcinoma 63 attain in a week. Tissue cul-

adduced in support of a causal relationship between nucleoproteins and growth stimulation.

We have not had available for this work any mammary tumor originating in mice of low-cancer strains. It would be premature, therefore, to conclude that the growth-stimulating property that we have found to be common to all mammary tumors of high-cancer strains is a distinctive feature of these tumors, or of mice possessed of genetic susceptibility for mammary cancer together with the milk factor. Such tumors are the only mammary carcinomas from mice of known genetic constitution that we have been able to investigate, and these are the only tumors that have induced a growth of fibroblasts 8 to 10 times greater than that of the controls. A squamous cell carcinoma that arose spontaneously in the skin of a C57 mouse has been found to stimulate fibroblastic growth rather more than carcinoma 63, but it would be unjustifiable to draw any conclusions from the study of a single

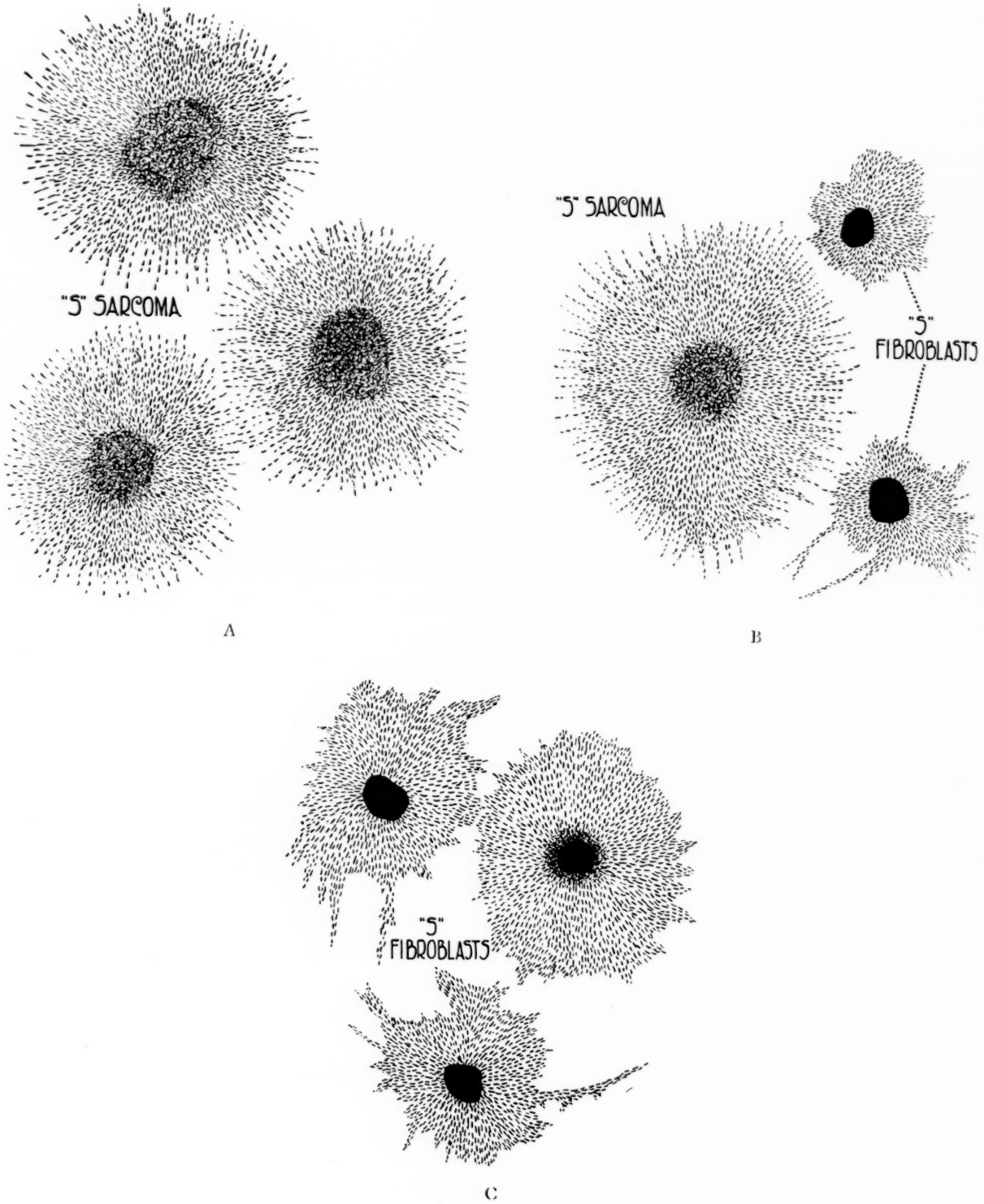

FIG. 9.—Semidiagrammatic tracings of 3 cultures after 6 days' growth, illustrating the inhibition of fibroblastic growth by a sarcoma. (a) Growth from 3 explants of an S sarcoma; (b) sarcoma with fibroblasts; (c) fibroblasts grown alone.

tumor originating in a tissue other than mammary gland.

Discussion of the significance of fibroblastic growth stimulation by mammary carcinomas of high-cancer strains will be postponed until our following paper, in which will be described the results of transplantation and explantation experiments with mammary tumors that have undergone sarcomatous transformation.

SUMMARY

1. The growth of mouse fibroblasts in tissue cultures is influenced by the proximity of other tissues.

2. A considerable stimulation of growth has been observed in the presence of the following tumors:—

(a) Spontaneous and transplanted mammary carcinomas of the high-cancer strains Strong A, C3H, and RIII.

(b) Mammary carcinomas induced in susceptible hybrids by the injection of dried RIII tumors.

3. Fibroblasts cultivated between 2 explants of these tumors grew more rapidly and were mitotically active over a longer period than those of control cultures, so that the maximum growth attained by cultures of the former was 8 to 10 times that of the controls in most experiments.

4. Fibroblastic growth was also stimulated to a lesser extent by cultures of embryo kidney and of the transplantable carcinoma 63. The latter is the most rapidly growing of the tumors employed in these experiments, hence it can be concluded that fibroblastic growth stimulation is not directly related to the rate of tumor growth.

5. Growth stimulation of fibroblasts occurred irrespective of: (a) their age, whether embryonic or adult; (b) their organ of origin, whether from heart, kidney, dermis, or mammary gland; (c) their genetic constitution, whether from high-cancer or low-cancer strains or from hybrids.

6. Sarcomas of both high-mammary and low-mammary-cancer strains of mice inhibited fibroblastic growth under the experimental conditions described.

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The Ascorbic Acid Content of the Liver in Pregnant Mice*

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In the course of an investigation upon the ascorbic acid content of the liver in mice (1), in which 121 females were examined, some high values in pregnant animals were noted, and this matter has been made the subject of a further inquiry comprising 109 female mice, of which 53 were pregnant.

METHODS

The mice were drawn from stock and MRC breeds, the characters of which are described in the previous paper (1), and from the pure lines C57, CBA, C3H, and dba. As far as was possible a pregnant and a nonpregnant mouse of any one breed, of similar age, were examined on the same day, as a safeguard against any variations due to the season of the year or to changes in the quality of the foodstuffs. The analyses were made, by visual titration, in the manner already described (1), except that a mechanical disintegrator was used in place of grinding by hand. This change in technic has not produced any constant change in the magnitude of the results for concentration of ascorbic acid in the liver (Table I); in some strains the mean is greater, in some less, in the new series. The order of the means is, for the 4 pure lines, the same in the old and new series. Thus the ascending order of all the means runs as follows:

Old series, nonpregnant	C57	Buff MRC	Stock	CBA	C3H	dba	
New series, nonpregnant	C57	CBA	Buff MRC	Brown MRC	C3H	Stock	dba
New series, pregnant	Brown MRC	C57	Stock	Buff MRC	CBA	C3H	dba

As regards the absolute amounts, the chief disparity in the pure lines is that between the old and new figures for C3H (322 and 274 γ per gm.), but the new series consisted of only 7 much younger mice.

Ascorbic Acid in the Liver

The results summarized in Table I show that the mean concentration of ascorbic acid in the liver is higher in the pregnant mice in each of the 7 strains. If this concentration in the nonpregnant mice is represented by 100, then in the corresponding pregnant series this figure ranges from 117 to 161. The difference is not significant in the stock ($P=0.35$), is probably significant in the Brown and Buff MRC and dba ($P < 0.05$), and is highly significant in the C57,

Table I: Ascorbic Acid and Glutathione in Liver

	Number		Ascorbic acid in liver, mean										Previous series (1), nonpregnant	
			γ per gm. liver				γ per gm. body weight		Total, γ		Glutathione. Mean cc. iodine $N/100$ per gm. liver			
Strain	Nonpreg.	Preg.	Nonpreg.	Preg.	Ratio Nonpreg. = 100	P	Nonpreg.	Preg.*	Nonpreg.	Preg.	Nonpreg.	Preg.	No.	Ascorbic Acid mean γ per gm. liver
Stock	6	5	295	345	117	0.35	15.2	18.3	416	728	1.09	0.92	7	224
Brown MRC	11	10	258	307	119	<0.05	13.7	16.8	352	561	0.98	0.82		
Buff MRC	5	4	252	351	139	<0.05	14.0	19.8	402	745	0.89	0.87	21	188
C57	10	9	216	336	156	<0.01	13.3	19.3	285	604	0.75	0.82	7	175
CBA	13	13	242	389	161	<0.01	12.7	21.6	227	608	0.91	0.85	37	257
C3H	7	9	274	410	150	<0.01	16.2	22.2	273	613	0.98	0.91	30	322
dba	4	3	336	509	151	<0.05	19.6	29.9	354	803	0.95	0.89	4	467
Total	56	53											106	

* Body weight includes weight of fetuses.

* Because of the difficulties of international communication the authors have not read proof of this article.

CBA and C3H ($P < 0.01$). No distinction between the strains of high (dba, C3H) and those of low mammary cancer incidence (C57, CBA) is seen in this respect. Unfortunately our stock of the RIII high-cancer strain has been too small to yield adequate material; the one pregnant mouse of this strain examined showed the highest concentration of ascorbic acid that we have ever found in the liver of a mouse, namely 641 γ per gm.

The means of the ages (range 67 to 788 days) in Table II show that the endeavor to make the two series comparable was fairly successful except in the case of the stock and MRC strains, in which mice of similar ages were not available. The position in regard to body weights is less satisfactory; the mean weight of the pregnant mice after removal of the fetuses was still 7 gm. greater than that of the nonpregnant mice. This may be due to (a) increase in weight of the uterus (with the addition of the placenta), mammary gland, liver (see below), and possibly of other organs as well, in pregnancy; and (b) the natural tendency to select the most robust-looking mice for breeding. However, this difference in the mean weights of the two series should not invalidate the comparison made here, since the full records from the nonpregnant mice show no regular relation between body weight and concentration of ascorbic acid in the liver.

TABLE II: RATIO OF LIVER WEIGHT TO BODY WEIGHT

Strain	Mean age, days		Mean weight, gm.					Mean liver weight, per cent of		
			Body			Liver		Body weight		Weight of body minus fetuses
	Nonpreg.	Preg.	Nonpreg.	Preg.	Body minus fetus	Nonpreg.	Preg.	Nonpreg.	Preg.*	
Stock	217	123	28.2	39.7	37.9	1.42	2.09	5.41	5.34	5.90
Brown MRC	538	230	25.9	34.2	30.7	1.37	1.85	5.29	5.45	6.05
Buff MRC	364	195	28.9	38.7	33.6	1.62	2.11	5.58	5.57	6.33
C57	257	264	21.0	30.8	28.2	1.27	1.82	5.98	5.91	6.48
CBA	152	196	18.2	28.6	25.2	0.97	1.58	5.31	5.60	6.13
C3H	127	128	17.2	25.1	23.0	1.01	1.48	5.91	5.94	6.43
dba	148	172	17.9	26.5	26.5	1.05	1.55	5.86	5.95	6.45

* Body weight includes weight of fetuses.

The sexual history of each mouse used had been recorded; the nonpregnant animals were classified as virgin, mated, and 1-, 2-, 3- . . . . up to 7-parous. Sexual conditions other than pregnancy do not appear to have any constant effect upon the concentration of ascorbic acid in the liver. Thus in the stock series the highest and lowest figures (176 and 432 γ per gm.) were given by two 3-parous mice. In the earlier series also "No constant differences were found between mice that had had no, or from one to five, litters" (1). The majority of the pregnant mice used were pregnant for the first time, but no constant difference was found between these and others that had had up to 6 previous litters.

We can present no exact data showing the relation of the ascorbic acid content to the stage of pregnancy reached; a much more elaborate investigation by the vaginal-plug method would be required for this purpose. Some indication of the stage of pregnancy was given by the total and mean weights of the fetuses, which were recorded in almost all cases. The smaller fetuses cannot be weighed accurately, owing to the difficulty of separation from the membranes. The value of the mean weight is of course affected by the very wide range of size often seen in a single litter *in utero* in the mouse. In the small series of C3H and dba mice the concentration of ascorbic acid is by far the smallest in the 2 mice in which the amounts of fetus could not be weighed, but elsewhere in the records, the publication of which would require too much space, no simple relation between these 2 quantities can be found.

GLUTATHIONE

The mean concentrations of glutathione (estimated by titration with iodine after the titration of ascorbic acid) are in 6 of the 7 series lower in the pregnant than in the nonpregnant mice (Table I). This provides evidence, additional to that presented in the two earlier papers (1, 2), that under various biological conditions glutathione and ascorbic acid do not behave in the same way.

RATIO OF LIVER WEIGHT TO BODY WEIGHT

The averages in Table II show that in pregnancy the ratio of the weight of the liver to that of the body (*i.e.*, body + fetuses) is approximately the same as the ratio in the nonpregnant female. Presumably this constancy of the ratio is maintained by growth of the liver proportional to that of the fetuses, and, in view of the very short gestation period in the mouse, this adjustment must be brought about quickly. If a mouse weighing 25 gm. produced 10 gm. of fetuses in 20 days, and the liver throughout this period made up 5.5 per cent of the whole, the liver must, if no

other factors are involved, maintain a mean daily gain of 0.0275 gm.

DISCUSSION

These results suggest inquiries as to the source, and function, of the additional ascorbic acid in the liver of the pregnant mouse. Three tissues associated with pregnancy, namely those of the fetus, of the placenta, and of the corpus luteum, suggest themselves as possible sources, and the last is known to be rich in ascorbic acid. Neither transference from the fetus to the mother, nor from the mother to the fetus, seems very well adapted to explain an increase by 50 per cent in the concentration in the liver.

During recent years a considerable amount of data has appeared on the destruction of estrogens in the liver, but we do not know whether ascorbic acid is concerned in this process nor whether increased amounts of estrogens are in circulation in the pregnant mouse. In the human body the effect of pregnancy in increasing the capacity to detoxicate synthetic estrogens seems to be considerable (3).

SUMMARY

The concentration of ascorbic acid in the liver has been compared in pregnant and nonpregnant mice, and in the pregnant condition an increase was found that was significant in 3, and probably significant in 3 more, of the 7 strains examined.

We are indebted to Dr. F. L. Warren for the examination by statistical methods of the material presented here. Mr. P. J. Ewers has provided an essential part of the data in the life histories of the mice under his care. This investigation has been assisted by generous financial grants from The British Empire Cancer Campaign and The Anna Fuller Fund.

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The Serial Passage of an Avian Lymphoid Tumor of the Chicken*

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Serial passage of other neoplasms has been associated with changes in the host-tumor relationship, such, for example, as the acquired ability of the Rous sarcoma to grow in hosts refractory to the tumor in its early transfers (6). Again, a more rapid rate of growth and a higher percentage of successful inoculations during serial transfer have been noted with other neoplasms of the chicken (1, 2, 4).

The present report is concerned with changes in growth capacity of a lymphoid chicken tumor observed during the course of its serial passage over a period of 3 years.

MATERIALS AND METHODS

The origin of the growth and its characteristics during 30 passages have been previously reported (5). Implants grow rapidly and may metastasize to distant organs. The tumor is not associated with fowl paralysis, and is different from neoplastic diseases caused by filter-passing agents such as chicken tumor I of Rous (6) and transmissible fowl leukosis (4).

Hosts for the tumor were derived from 3 stocks of Rhode Island Red chickens. Stock A, most often used, was derived from an inbred group in which an attempt has been made to obtain stock more homogeneous than that ordinarily available. Brother-to-sister matings were made for 3 successive generations, as well as matings of less closely related members of the stock. Stock A was more homogeneous during the latter period of its use than during the earlier period. Stock B came from the same flock that supplied the progenitors of stock A; however, the actual relation between stocks A and B was slight. Stock B was uniform over the different periods of use, for progeny from only one pen mating were used during any one period of time. Stock C was obtained from a commercial flock and was unrelated to stocks A and B. All chickens were hatched from eggs in the laboratory and raised under uniform conditions. The birds were maintained in battery cages under essentially similar conditions throughout the period of observation. Most of them were between 4 and 8 weeks old when inoculated with tumor.

A standard method was followed for the preparation of the inoculum. Under the usual aseptic precautions part of a tumor resulting from an intramuscular implant was minced and added to an equal volume of modified Rous-Turner solution, Ringer's solution made isotonic for bird erythrocytes (3). One part of infusorial earth was then added to 1,000 parts of this mixture, and half a milliliter of the final product was injected with a syringe and 15-gauge needle into the breast, or occasionally into the muscles of the thigh.

A single line of serial transfer was maintained from the 30th to the 44th transfer. During this time no attempt was made to conform to a standard interval between transfers; however, the interval averaged 14.9 days. Beginning with the 45th transfer 2 separate lines were begun. The one line was to be transferred to a new host every 10 days; the other every 15 days. The interval for the "10 day" series averaged 9.3 days through the 132nd transfer, and for the "15 day" series 14.8 days through the 100th transfer.

On 3 occasions the serial passage with fresh tissue was interrupted: (a) At the 42nd transfer the tumor failed to grow from the usual material and tumor that had been frozen 6 days at $-6°$ C. was used. (b) The chickens intended for the 50th transfer of the 10 day series developed an unrelated infectious disease after receiving the inoculation in the customary way. Another group had received liver infiltrated with tumor from a chicken of the 49th passage, and the growth in one of these was employed to continue the series. (c) The tumors in birds of the 83rd transfer of the 15 day series became infected with anaerobic gas-producing bacteria. In order to eliminate this contaminating organism, whole blood from a chicken with diffuse metastasis of the tumor was used to produce growth in the birds bearing the 84th transfer of the tumor. This was possible since tumor cells are commonly found in the blood of chickens with diffuse metastasis.

The chickens were kept for varying periods of time

* Contribution No. 526 of the Massachusetts Agricutural Experiment Station.

following inoculation. The site of the implant was examined weekly, and birds in which no growth was observed after 3 to 4 weeks were either killed or used in other experiments 2 to 3 weeks after regression of the tumor. Chickens in which the tumor grew progressively were killed when moribund, or to obtain material for inoculation, or allowed to die. No chicken that lived for less than 8 days after inoculation was considered in the tabulation of results.

A postmortem examination was made on all birds employed, and tumor, liver, spleen, kidney, adrenal, bone marrow, and thymus gland of birds supplying material for transplantation were routinely examined by histological section. Histological examination was made, also, of all doubtful lesions.

Reaction of Host

Following tumor inoculation, one of 5 things was found to happen: (a) The implant failed to grow; (b) a short period of growth was followed by regression; (c) growth continued at the inoculation site until the death of the host; (d) the tumor grew at the site of implantation and localized metastatic foci were found in the viscera; or (e) the implant grew and a diffuse type of metastasis was found in the internal organs.

Failure to grow.—In chickens killed 2 weeks after inoculation, where no growth was observed, a small amount of localized fibrosis was present at the site of implantation, which had almost completely disappeared in birds killed at the end of 3 weeks.

Growth and regression.—Maximum growth was usually noted about 2 weeks after inoculation. Rarely did regression occur after 3 weeks of continuous growth. Growth and regression was noted in approximately one-fourth to one-half of the birds inoculated.

That the growths in this group contain living tumor cells for a time is shown by the following instance. A biopsy was made on a tumor (bird N96) that developed from an implant received 12 days previously. The inoculum prepared from the excised material developed in all 6 chickens into which it was implanted and metastasized in 4 of them. The tumor of N96 began to regress after the biopsy and only a slight fibrosis remained at the site when the bird was killed 71 days later. However, biopsy did not consistently lead to regression in other tumor-bearing birds.

The rapid loss of activity of a tumor in a state of regression is suggested by a case in which maximum growth was noted 11 days after an implant was received. The bird (N247) was killed 4 days later and the somewhat necrotic tumor tissue inoculated into 5 chickens, which had received active tumor material from another donor 3 days earlier. The active tumor material grew in all 5 birds, whereas no growth occurred with the material from N247. It should be pointed out, however, that the experiment is not conclusive, because the first injection may have produced some resistance.

Local growth.—This group includes all birds in which there was progressive growth of the implant until death. As previously reported, the limit of growth seemed to be about one-fifth the body weight in hosts bearing the tumor at only one implantation site. In general, relatively larger tumors developed in the younger birds. In some instances the growth amounted to more than one-fourth the body weight; for example, in a male chicken that weighed 475 gm. at death a tumor developed in 42 days that weighed 135 gm., or 28.4 per cent of the body weight. A larger total amount of tumor developed in birds in which multiple implants were made. This is exemplified in the case of a 28 day old male chicken that received implants of tumor in both breast muscles and died 18 days later; the carcass weight was 272 gm. and the combined weight of both tumors was 99.5 gm., or 36.5 per cent of the body weight.

A variable amount of necrosis was commonly found in the tumors, usually in and about the fascia separating the superficial and deep pectoral muscles. The margin between viable and necrotic tissue was usually discrete (Fig. 1). In some instances a large tumor was almost entirely involved by dry necrosis, and in such cases the bearers were often dull and listless and refused to eat, perhaps because of an intoxication. Attempts to isolate a bacteria from necrotic tumors failed. In some instances necrosis may have been caused by ischemia following growth of the neoplasm about blood vessels; in others by a mechanism similar to that which operates in the regression of implants 2 weeks after inoculation.

Growth with localized metastasis.—In this group are included those chickens in which the implant grew and localized metastatic foci were found in the viscera; their general nature has been previously described and illustrated (6). The organs most frequently involved were the proventriculus, heart, pancreas, adrenal, and gonads; the kidney, spleen, thymus, marrow, peritoneum, lung, and liver were less often affected (Table II).

The assembled data were examined for differences between birds that were killed and those that died. The heart was involved in 61.5 per cent of the 73 birds that died with metastases, but in only 22.4 per cent of the 54 birds that were killed. Death may be accounted for by the mechanical effect of the tumor on the heart. The relatively more frequent involve-

ment of the proventriculus and pancreas in birds that died is more difficult to explain, and may not be significant; however, the birds that died lived an average of 4.3 days longer than those that were killed; so that there was more time for metastatic foci to develop. Somewhat more frequent involvement of the spleen. thymus, bone marrow, and lung was noted in birds

TABLE I: SUMMARY OF RESULTS OF SERIAL PASSAGE OF A LYMPHOID TUMOR

	Passages 1 to 30	Passages 31 to 44	Passages 45 to 100 (15 day interval)	Passages 45 to 132 (10 day interval)
Number of birds inoculated	347	151	301	444
Reactions:				
No growth	32.6 *	4.0	1.7	1.3
Growth and regression	23.9	49.0	40.2	30.7
Local growth only	29.1	34.4	22.2	15.9
Growth with localized metastasis	14.4	11.9	24.6	7.8
Growth with diffuse metastasis	...	.7	11.3	44.3

* Expressed in per cent of number inoculated.

TABLE II: RELATIVE INCIDENCE OF LOCALIZED METASTASIS IN VISCERA: PASSAGES 31 TO 132

	Total	Died	Killed	♂	♀
Number of cases	127	73	54	80	47
Duration of experimental life (days):					
Average	19.7	21.4	17.1	19.2	20.8
Longest	47	47	35	37	47
Shortest	9	10	9	9	10
Organs affected:					
Proventriculus	54.3 *	64.4	41.5	57.5	48.8
Heart	44.1	61.5	22.4	42.5	46.8
Pancreas	41.7	55.0	24.1	45.0	36.2
Adrenal	40.1	37.0	44.5	41.5	38.4
Gonad	26.0	28.8	22.4	31.3	17.0
Kidney	15.7	14.1	13.0	16.2	14.9
Spleen	14.2	5.5	26.0	13.7	14.9
Thymus	13.4	8.2	20.4	16.2	8.5
Marrow	8.7	4.1	14.8	7.5	10.6
Peritoneum	5.5	5.5	5.6	5.0	6.4
Lung	3.9	...	9.3	3.7	4.2
Liver	2.4	1.4	3.7	2.5	2.1

* Per cent of number of cases.

that were killed (Table II). Metastatic foci in these organs were often found only by microscopic examination (Fig. 2). The data may be somewhat vitiated by the fact that a routine histological examination was made more often in birds that were killed.

The testes were found affected more often than the ovary, a difference that is believed significant since other organs, with the possible exception of the thymus, were involved at about the same rate of frequency in males as in females (Table II).

In most instances 3 organs or less were involved by localized metastasis. In 127 instances only 1 localized focus was found in 2.68 per cent; 2 organs were involved in 26.8 per cent; 3 organs in 19.6 per cent; 4 organs in 10.2 per cent; 5 organs in 10.2 per cent; and 6 organs in 5.5 per cent of the cases.

The most widespread metastasis occurred at the 52nd transfer in a male host (N494) 42 days old at the time of inoculation; the bird was killed 21 days later. Metastatic foci were found in the heart, proventriculus (Fig. 3), pancreas, testes, one adrenal, bone marrow, and kidney, and the diagnosis was confirmed by histological examination. No essential differences were found in the number of organs involved by metastasis that could be attributed to sex, to whether the birds died or were killed, or to the number of times the tumor had been transferred.

The earliest localized metastasis was found in the bone marrow of a chicken killed 9 days after receiving implants of the tumor in both breast muscles and the right thigh muscles. In 4 instances metastasis was observed 10 days after inoculation, and in one of these microscopic metastatic foci were present in two organs (kidney and adrenal). Only 10 of the 127 cases of localized metastasis occurred in birds examined after an interval of less than 14 days following inoculation.

Growth with diffuse metastasis.—This type of reaction represented the most fulminating and violent disturbance following implantation of the tumor. Only a few such cases were noted in the earlier passages of the tumor, but they became more common later on. The characteristic of this reaction was death of the host in about 8 to 12 days after inoculation, often sudden after a brief period of depression that usually lasted only a few hours. Occasionally an entire group would die in this way before material could be obtained for the next transfer at the previously selected interval of 10 or 15 days. The implants themselves were no larger than in other hosts at this stage. Visceral changes usually consisted of a notable enlargement of the liver, spleen, and occasionally the kidneys (Fig. 4). The bone marrow was usually hyperplastic and grey-red in appearance.

The weight of the liver varied from 5.3 to 12.1 per cent of the body weight in a series in which these weights were recorded. The most enlarged liver in this series weighed 59.5 gm. and was found in a chicken that died 9 days after inoculation. The carcass weight at death was 492 gm., and the bird was 50 days old at the time of inoculation. In some instances the size and weight of the liver were within normal limits. The color was usually red-brown. Histologically the neoplastic lymphoid cells seemed to occupy an extravascular position beneath the endo-

FIGS. 1–5

thelium of the sinusoids, although some were found within them. These cells tended to proliferate in some localized areas about blood vessels, but not always in direct connection with the periportal areas (Fig. 5). There was usually considerable crowding and distortion of the liver cells, many of which were in various stages of degeneration.

The weight of the spleen varied from 0.60 to 1.88 per cent of the body weight. The organ was usually

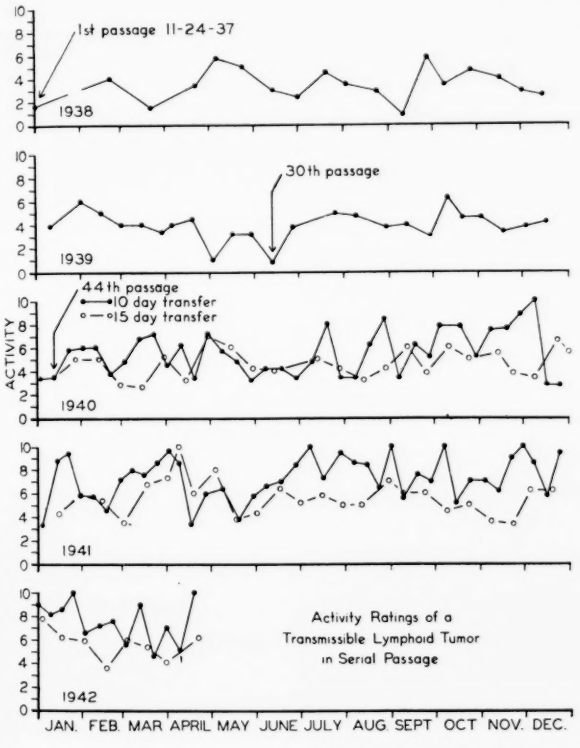

FIG. 6.—Serial passage of a transmissible lymphoid tumor.

a purple-red color, its capsule tense, and the pulp was filled with neoplastic lymphoid cells.

The histology of the bone marrow was essentially of the order found in the liver and spleen; namely, an overcrowding of the parenchyma with large neoplastic lymphoid cells similar to those of the implant.

The large lymphoid cells were often, but not always, found in the vascular bed of other organs such as the kidney, lung, heart, and thymus.

The pathogenesis of this reaction is not entirely clear. The lymphoid tissues of the liver, spleen, bone marrow, and sometimes the kidney, may have been stimulated to hyperplasia by a hypothetical agent liberated from the neoplastic implant; or, as in mouse leukemia, the lesions may have resulted from the proliferation of cells transferred there.

Effect of Serial Passage

As shown in the preceding paragraphs the growth capacity of the tumor may vary, since in different birds the implanted cells either fail to grow, grow temporarily, or grow progressively with or without metastases. It was found that the growth capacity changed with serial passage, in that there was a general increase in the activity of the tumor. To illustrate this change more clearly, data previously reported (5) on passages 1 to 30 are used in the following discussion.

The relative number of birds in which the implant failed to grow decreased with passage of the tumor. In the first 30 passages 32.6 per cent were refractory to the tumor, whereas a much smaller percentage (4.0 per cent) were refractory during the 31st to 45th passages. The relative number in succeeding passages was still less, being 1.7 per cent in the 45th through the 100th passage, made at 15 day intervals, and 1.3 per cent in the 45th through the 132nd passage, made at 10 day intervals (Table I).

The relative number of chickens in which growth was followed by regression was high in the 31st to 44th passage, perhaps because of a shift from the "no growth" group. Their relative number, however, decreased in subsequent passages. There was a similar decrease in the relative number of birds with local growth only. More instances of metastasis were observed in the 31st through the 132nd passage than during the first 30 passages. The most definite increase was in the relative number of cases of diffuse metastasis during the 45th through the 132nd passage at 10 day intervals. Localized metastasis was observed most frequently during the 45th through the 100th passage, at 15 day intervals.

A method for evaluating the activity of the tumor during its serial passage was devised, in which a numerical value was attached to the reaction obtained

DESCRIPTION OF FIGURES 1 TO 5

FIG. 1.—Sagittal section of a 22 day old tumor in pectoral muscle, about two-thirds necrotic. Weakness, loss of appetite, metastases in heart, pancreas, testes, kidney, and proventriculus. This tumor occurred in the 62nd passage of the "10-day series."

FIG. 2.—Microscopic metastatic foci in spleen, which was only slightly, if at all, enlarged. Mag. × 44.

FIG. 3.—Proventriculus with localized metastasis in chicken N494. Note infiltration of tumor between glandular acini and in muscularis. Mag. × 104.

FIG. 4.—Enlarged liver and spleen, femur, and 11 day old tumor in pectoral muscles. Characteristic diffuse metastasis. Marrow cavity largely filled with tumor.

FIG. 5.—Liver of bird that died with diffuse metastasis 11 days following inoculation. Isolated islands of liver cells are apparent. Congested vein at right contains many tumor cells, and extravascular growth of the tumor is evident at each side of the vein. Mag. × 346.

in each host. No growth was rated as 0; growth followed by regression as 3; local growth only as 5; growth with local metastasis as 7; and growth with diffuse metastasis as 10. This system of grading, based on purely arbitrary considerations, represents an evaluation of the interplay between the activity of the tumor and resistance of the host, and therefore reflects the sum total of factors that influence both the tumor implant and the host. The average activity ratings of the hosts for each passage are plotted in Fig. 6 according to years. When plotted in this way the data do not form a straight line, but rather are notable for distinct differences from one passage to the next. There were some periods when the activity ratings would tend to form smooth lines, but attempts to correlate them with the season of the year or a specific stock of chickens were unsuccessful. In general the activity rating of the tumor was higher when it was transferred at 10 day intervals than at 15 day intervals. There were periods, as from the latter part of April to the early part of July, in 1940, and the latter part of March to the middle of June, in 1941, when the activity of these two lines of transfer tended to parallel each other. The factor or factors responsible for this are not clear. There was a trend toward higher activity associated with successive serial passage.

Effect of Sex on Reaction of Host

In earlier work with this tumor the sex of the host seemed to have no effect on the result of the implant (5), but in subsequent serial passage it appeared that sex may be a factor. The sex ratios of the different groups in passages from 31 through 132 were examined with the following results, in which ratio is expressed as ♂/♀:

Failure to grow	16	birds	ratio 1/1
Growth and regression	278	"	" .93/1
Local growth	190	"	" 1.51/1
Growth with localized metastasis	127	"	" 1.70/1
Growth with diffuse metastasis	229	"	" .94/1
All birds	840	"	" 1.036/1

In 56 instances sex was not recorded and these could not be included. A relatively higher ratio of males to females was noted in birds with local growth only and birds with growth with localized metastasis (ratios of 1.51/1 and 1.70/1, respectively) than in all birds (ratio 1.036/1). In the other three groups, the ratio of males to females was essentially similar to that of all birds.

DISCUSSION

The reactions of hosts bearing this lymphoid tumor seem to fall into a distinctive pattern, which can be interpreted as the result of interplay between the activity of the implant and the resistance of the host. Thus the respective reactions of no growth, growth and regression, local growth only, growth with local metastasis, and growth with diffuse metastasis represent either decreasing degrees of resistance in the host or increasing degrees of activity in the tumor implant, or both. Which is the more important factor must be determined by the circumstances of each particular case. Failure of an active inoculum to grow, or its regression, suggest resistance of the host, whereas progressive growth and diffuse metastasis suggest either the lowest degree of host resistance or the acme of activity in the inoculum. Since the same tumor material injected into a group of chickens provoked different reactions in different birds, it must be assumed that the implants encountered varying degrees of resistance to their growth.

The hosts were essentially the same in all transfers; hence the increased activity of the tumor implants must have been due to serial transfer. This enhancement of growth ability was more pronounced with transfers made at 10 day intervals than with transfers made at intervals of 15 days.

CONCLUSIONS

1. The reaction of a chicken after receiving an implant of the lymphoid tumor herein described will vary depending upon the activity potential of the tumor and the resistance of the host.

2. In ascending order of severity these reactions are: failure of the graft, growth and regression, progressive local growth only, growth with localized metastasis, and growth with diffuse metastasis.

3. Serial transfer of the tumor enhanced its ability to produce the more severe reactions.

4. Transfer of the tumor at 10 day intervals was more effective in raising the growth activity of the tumor than transfer at 15 day intervals.

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Abstracts

Experimental Research, Animal Tumors

Zur Entstehung krebserzeugender Substanzen beim Menschen [Production of Carcinogens in Human Beings.] Druckrey, H., Richter, R., and Vierthaler, R. [Pharmakol. und Hyg. Inst. Univ., Berlin, Germany] *Naturwissenschaften,* **29**:63-64. 1941.

The authors report preliminary experiments and discuss the possible action of intestinal bacteria in the production of carcinogens from substances related to the bile acids. *B. coli* was obtained from the feces of a patient with rectal cancer and grown on Sauton's peptone medium. To the series of cultures in Group I, 5 mgm. per cent dehydronorcholen was added; to Group II, 5 mgm. per cent desoxycholic acid; Group III served as control. All cultures were kept for 24 hours in an incubator, then extracted with benzol, the extracts evaporated *in vacuo,* and the residue dissolved in 20 cc. peanut oil. Three groups of 6 rats each received 6 biweekly injections of the peanut oil solutions. Control experiments were done with pure peanut oil, with dehydronorcholen irradiated by ultraviolet light, and pure and irradiated desoxycholic acid dissolved in peanut oil in concentrations of 100 mgm. per cent. In Group I, 18 months after the last injection, a sarcoma at the site of injection was noted in 1 animal. After 22 months 1 rat with an intra-abdominal tumor and 1 with multiple sarcomas were observed. In 1 control rat that received ultraviolet irradiated dehydronorcholen an intra-abdominal sarcoma was seen. No other tumors were found in any of the other groups although a few animals lived longer than 18 months.—K. D.

Charakterisierung und Mechanismus der Krebs erzeugenden Kohlenwasserstoffe. [Characterization and Mode of Action of the Carcinogenic Hydrocarbons.] Schmidt, O. [Ziegelhausen bei Heidelberg, Germany] *Naturwissenschaften,* **29**:146-150. 1941.

The faculty of certain aromatic hydrocarbons to produce skin cancer is attributed to loosely bound electrons, called B-electrons. These electrons are not only responsible for the chemical and most of the physical properties of these substances but, when brought in intimate contact with living cells, induce chemical changes, such as racemization and splitting of the tissue proteins. These changes in the cellular proteins lead to the production of carcinogenic viruses or cell necrosis. The reasoning of the author is purely speculative; no experimental evidence in support of these sweeping conclusions is presented.—K. G. S.

Wirkt der Russ von Oelfeuerungen karzinogen? [Is Fuel Oil Tar Carcinogenic?] Miescher, G., and Schwarz, F. [Universitätsklinik, Univ. Zürich, Zürich, Switzerland] *Schweiz. med. Wchnschr.,* **72**:1081-1082. 1942.

A concentrate painted on 100 male mice twice weekly for 167 days, or until a total of 50 applications had been made, produced not the slightest change in the skin, nor was any toxic effect apparent. On the 272nd day, when 12 mice were still living with not even a papilloma among them, the experiment was terminated.—W. H. W.

Effects of South Wales Anthracite Coal and of Precipitated Amorphous Silica upon the Lungs of Mice. Campbell, J. A. [National Inst. for Med. Research, Hampstead, England] *Brit. J. Exper. Path.,* **25**:46-55. 1944.

Mice were exposed to various dusts, (1) anthracite, (2) Al_2O_3, (3) SiO_2, (4) Al, (5) MgO, (6) bituminous coal, (7) cigarette smoke, and to various combinations of these, making 11 forms of dust in all. Significant increases in lung tumors occurred only under the action of SiO_2, Al_2O_3, or Al. Anthracite gave no increase, and bituminous coal one of border-line significance. The mean number of lung tumors per mouse with a lung tumor was 1.3 (control) and 1.4 (experimental), and the mean maximum number of lung tumors in any one mouse was 1.5 (control) and 2.4 (experimental). The maximum number of tumors in any one mouse was 4, in a control. "Usually the dusting experiments which show an increase in incidence of lung tumours show also an increase in the proportion of tumours which are malignant, and also an increase in size of the tumour. . . . . Size of tumour increases with malignancy and age, and eventually a whole lobe may be involved." The largest tumor in dusted mice was 8×8 mm., and in control mice was 4×4 mm. Alcohol in the drinking water up to 5% did not affect the results; mice drank less of this beverage than of pure water. The following paragraph has been appended to the paper "Dr. Campbell's death occurred while this paper was in the Press. It seems desirable to place briefly on record the results obtained in guinea-pigs exposed to anthracite dust under the same conditions as the mice. Six guinea-pigs were killed after being exposed over a period of 4 years and five others after 3½ years. All showed extensive deposition of coal-dust in the lungs; one only, one of those dusted for 3½ years, showed in addition a localized adenomatous proliferation of bronchial epithelium, probably attributable to the dusting."—E. L. K.

Experimentelle Geschwulsterzeugung durch Einatmung von Radiumemanation. [Experimental Production of Tumors by Inhalation of Radium Emanation.] Rajewsky, B., Schraub, A., and Kahlau, G. [Kaiser Wilhelm-Instit. Biophysik und Senckenbergisches Path. Instit. der Univ., Frankfurt a. M., Germany] *Naturwissenschaften,* **31**:170-171. 1943.

Microfilm copies of such papers here abstracted as are available may be obtained from Medicofilm Service of the Army Medical Library at 25¢ for each complete article, not exceeding 25 pages in length—and 10¢ for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.

The etiology of the Schneeberger and St. Joachimsthaler disease of miners has not yet been clarified. After 15 to 18 years' work in the mines, 50 to 80% of the miners die of cancer of the lung. It has been suggested that this might be caused by the action of radium emanation present in the air of the mines, but no proof has been given. A report of the "Radioactive climate" in the mines has already been published (Rajewsky, B., *Ztschr. f. Krebsforsch.*, **49**:315-340. 1939). The present paper reports on experiments performed on mice exposed to known amounts of radium emanation mixed with air: the general behavior, weight, blood picture and postmortem histology were investigated. The minimal toxic amount of radium was found to be 1×10^{-8} to 2×10^{-8} Curie per ccm.; in 3 experiments in which 36 mice were exposed to 37,500, 44,200, and 55,700 ME, the animals showed rapid loss of weight, abnormal blood pictures, and died after 60 to 100 days. Histological examination revealed atypical bronchial epithelium. After exposure to 1.16×10^{-9} Curie per ccm. (3,200 ME), the animals lived for from 161 to 453 days (average 286). Seventy-five per cent of the control animals lived longer. In each of the 12 treated animals, atypical bronchial epithelium was found, including 10 adenomas, 1 adenocarcinoma, and 1 small cell malignant blastoma. In the controls at the end of 460 days, only 1 animal had a small adenoma. The production of the adenomas depended upon the duration of exposure to the inhalation of radium emanation.—K. D.

Prüfung auf das Vorkommen von d-glutaminsaüre in Eiweiss von malignen Tumoren und von normalen Organen. [The Occurrence of *d*-Glutamic Acid in Proteins from Malignant Tumors and from Normal Organs.] Abderhalden, E. [Physiol. Inst. d. Univ. Halle a. S., Halle a. S., Germany] *Ztschr. f. physiol. Chem.*, **275**:135-154. 1942.

The glutamic acid from hydrolyzates of different normal tissues and human carcinomas was isolated as hydrochloride. The first crystallizates from concentrated hydrolyzates were repeatedly recrystallized until the elementary analysis indicated sufficient purity. All mother liquors were preserved, combined, and the glutamic acid isolated by fractional distillation as diethylester. After saponification the hydrochloride of the acid was recovered by crystallization. The crystallized fraction of all typical tissues and of most tumors showed rotation typical for *l*-glutamic acid. In 2 tumors small amounts of *d*-glutamic acid were found. The values were much lower than those reported by Kögl.—Z. D.

Über die Glutaminsaüre aus Tumoren. [Glutamic Acid from Tumors.] Wieland, T. [Kaiser Wilhelm-Inst. Med.-Forschg. Inst. Chem., Heidelberg, Germany] *Ber. d. deut. chem. Ges.*, **75**:1001-1007. 1942.

In order to examine the validity of Kögl's claim, that tumor proteins are characterized by a large content of *d*-glutamic acid, the glutamic acid from 4 different rat tumors, the Brown-Pearce rabbit tumor, and liver metastases from a human being with tumor was isolated by crystallization as hydrochloride. The method of isolation was a new one, published previously by the author (*Ztschr. f. physiol. Chem.*, **272**:24. 1942). It consists in adsorption of all dicarboxylic amino acid in an acid Al_2O_3 column. Cystine, which interferes, is removed by reduction with H_2S. The dicarboxylic acids are diluted by $Ba(OH)_2$. After the Ba is removed, the solution is then concentrated, *in vacuo,* and glutamic acid crystallized as hydrochloride. The mother liquor is strongly concentrated, and the crystallization repeated. If *d*-glutamic acid were present in the hydrolyzate the second crystallization should be much richer in it than the first one. But the glutamic acid of the second crystallizate was up to 99% *l*-glutamic acid. The lower rotation of the first crystallizate is due to some impurity and not to *d*-glutamic acid.—Z. D.

Über das optische Verhalten der im Eiweiss von Carcinom und seinen Metastasen und dem Muttergewebe enthaltenen Glutaminsaüre. [Optical Behavior of the Glutamic Acid Present in the Proteins from Carcinoma, its Metastases, and its Mother Tissue.] Abderhalden, E. [Physiol. Inst. d. Univ. Halle a S., Halle a. S., Germany] *Ber. d. deut. Chem. Gesellsch.*, **75**:1800-1802. 1942.

Further evidence against Kögl's conception of the role of *d*-glutamic acid in tumor formation. The glutamic acid from the hydrolyzates of a human stomach cancer, its liver metastases, and the healthy stomach and liver tissue of the same individual was isolated. The method was the same as that previously used by the author in similar investigations. (*Ztschr. f. physiol. Chem.*, **275**:135. 1942.) Only the *l*-form was found.—Z. D.

Über die Bestimmung von d-Glutaminsäure in Tumorhydrolysaten mit Deuterium als Indicator. 9. Mitteilung über die Chemie der Tumoren. [The Determination of *d*-Glutamic Acid in Tumor Hydrolyzates with Deuterium as the Indicator. 9. The Chemistry of Tumors.] Kögl, F., Erxleben, H., and van Veersen, G. J. [Rijks-Univ., Utrecht, Holland] *Ztschr. f. physiol. Chem.*, **277**:251-283. 1942-43.

The controversy that arose following the announcement by Kögl and Erxleben several years ago that tumor proteins contain an appreciable amount of the "unnatural" amino acid antipodes, particularly of *d*-glutamic acid, prompted the present authors to reinvestigate the problem with the aid of a new analytical method. The principle of this technic consists in the addition of an isotope-containing amino acid to a protein hydrolyzate, subsequent isolation of this amino acid by the usual methods, and determination of the isotope content of that fraction. From the dilution of the isotope content the concentration of the amino acid under investigation in the protein may be calculated (Ussing, H. H., *Nature, London,* **144**:977. 1939). With deuterium and the N^{15}-isotope used as the indicator, this technic has yielded results in the hands of R. Schoenheimer and his group (cf. Graff, S., Rittenberg, D., and Foster, G. L., *J. Biol. Chem.*, **133**:745. 1940) that seem to contradict Kögl and Erxleben's findings with regard to the abnormally high *d*-glutamic acid content in tumor tissue. The present authors have applied the "isotope dilution" method of analysis to a large series of tissues (Brown-Pearce, benzpyrene, Flexner-Jobling, human lung, and liver tumors; normal rat and rabbit tissues; and spleen from a patient with lymphatic leukemia), using deuterium-containing glutamic acid as the indicator sub-

stance. The result of the experiments, which are described in detail, is that, in confirmation of the previous claims of the present authors, the content in *d*-glutamic acid is a characteristic constant of the type of tissue examined: Normal tissues contain at best minimal amounts, while benign tumors contain 3 to 4% racemized glutamic acid; Flexner-Jobling carcinoma, 17%; methylcholanthrene and benzpyrene skin tumors, 22 to 27%; tumor metastases in human beings, 42 to 44%; and metastases from the Brown-Pearce tumor, 40 to 48%.—K. G. S.

Glutaminsäure aus Tumoren. [Glutamic Acid from Tumors.] KLINGMÜLLER, V. [Physiol.-chem. Inst. Univ. Berlin, Berlin, Germany] *Ztschr. f. physiol. Chem.*, **278**: 97-119. 1943.

This careful study was undertaken for the purpose of investigating the claim of Kögl and his collaborators that the protein of tumors contains "unnatural" *d*-amino acids, especially *d*-glutamic acid, in appreciable amounts. The results showed that *d*-glutamic acid could not be found in the protein fraction of malignant tumors in amounts large enough to permit attributing to it a significant function as a constituent of this type of tissue. The total glutamic acid fraction isolated from tumor tissue contained at the most 5.6% of the *d*-form, corresponding to 0.2 to 0.3% as calculated on the basis of the total dry protein.—K. G. S.

Ueber die Verdaulichkeit von Tumorgewebe durch normale Enzyme. III. Mitteilung: Versuche zur Isolierung von Glutaminsaeure auf enzymatischem Wege. [The Digestibility of Tumor Tissue by Normal Enzymes. III. Experiments on the Isolation of Glutamic Acid by Enzymatic Methods.] BAYERLE, H., and BORGER, G. [Pathol. Inst. Univ. München, Munich, Germany] *Biochem. Ztschr.*, **316**:87-95. 1943.

Kögl and Erxleben, in their well-known experiments on the isolation of "unnatural" amino acids, especially *d*-glutamic acids, from tumor tissue, employed hydrochloric acid for the hydrolysis of the tissue proteins. This has led to the assumption, on the part of some critics, that the HCl is responsible for the partial racemization of the glutamic acid, originally present solely in the natural *l*-form. For this and other methodological reasons, the present authors subjected liver metastases from a human being with carcinoma to successive enzymatic digestion by Cudahy pepsin at pH 1.8, by papain at pH 5.0, and by pancreatic trypsin, activated with enterokinase, at pH 8, after drying the tumor tissue with alcohol and heating to 90°C. for 30 minutes in order to destroy the enzymes present in it. Finally the material was subjected to the action of a fresh rabbit kidney extract containing active dipeptidase. In order to separate the amino acid antipodes that might be present in the hydrolyzate, the proteolytic digestion was followed by a treatment with fermenting yeast (Strain 138 Rotterdam neu, Brewing Experiment Station, Munich), which would be expected to destroy only the natural form of glutamic acid. Attempts to isolate from the hydrolyzate glutamic acid hydrochloride in crystalline form failed, even after seeding with *d,l*-glutamic acid-HCl.—K. G. S.

Manometrischer Nachweis von d-Peptidasen im Serum mit Hilfe von d-Aminosäureoxydase. [Manometric Determination of *d*-Peptidases in Serum with the Aid of *d*-Amino Acid Oxidase.] HERKEN, H., and ERXLEBEN, H. [Univ. Köln, Cologne, Germany, Rijksuniv., Utrecht, Holland] *Ztschr. f. physiol. Chem.*, **269**:47-55. 1941.

As substrate for the demonstration of *d*-peptidase action either *d*- or *d,l*-leucylglycylglycine was used. When this tripeptide has been split by *d*-aminopolypeptidase into *d*-leucine + glycylglycine, the degree of cleavage can be ascertained by measuring the oxidation of the *d*-leucine under the influence of kidney *d*-amino acid oxidase in the Warburg manometer. An examination by this method was made of 33 different normal and pathological sera. A cleavage of at most 6.6% of the substrate was shown by the sera from the 17 cancer patients. The other pathological sera showed either no cleavage or no more than 1.2% (anemia). All 3 normal sera tested were negative.—K. G. S.

Ueber die Fähigkeit des normalen Organismus, d-Peptide zu spalten. VI. Mitt. Zur Kenntnis tierischer Peptidasen. [Ability of the Normal Organism to Split *d*-Peptides. VI. Animal Peptidases.] MASCHMANN, E. [Forschungsinst. f. Chemotherapie, Frankfurt a. M., Germany] *Naturwissenschaften*, **29**:518-519. 1941.

The claim of Waldschmidt-Leitz and Mayer (*Ztschr. physiol. Chem.*, **262**:IV. 1939) that only the carcinomatous organism is capable of splitting *d*-peptides, is probably untenable. The author points out that the tests for the presence of certain dipeptidase and aminopolypeptidase activities may be rendered much more sensitive by the addition of certain metal salts (Mg, Co, Fe, Mn, Zn) with and without cysteine. When glycerol extracts of the intestinal mucosa, liver, and kidney of normal rabbits and guinea pigs as well as of chick embryos are examined in this manner, it is found that glycyl-*d, l*-leucine and glycyl-*d, l*-alanine are almost completely split in the presence of *M*/5,000 Zn while *d*-leucyl-glycine is strongly attacked in the presence of *M*/1,000 Mn and *M*/100 Mg. The author believes that the splitting of *d*-peptides stands in no causal relation to cancer, but that it represents a property of the peptidase enzyme system of normal organisms.—K. G. S.

Erniedrigte d-Aminosaüreoxydase-Wirksamkeit im Organismus tumorkranker Ratten. [Decrease in the *d*-Amino Acid Oxidase Activity in the Organs of Tumor-Bearing Rats.] WESTPHAL, U. [Inst. f. Physiol. und Wehrchem. d. Militärärztl. Akad., Berlin, Germany] *Ztschr. f. physiol. Chem.*, **276**:191-204. 1942.

The *d*-amino oxidase activity in the presence of *d*-phenylalanine of extracts of liver and kidney from normal rats and from those with Walker carcinoma was measured by O_2 consumption in the Warburg apparatus. The organs were ground with silicon and extracted with *M*/5 phosphate buffer of pH 8. The pH was adjusted to 7.8 and the experiment run for 3 hours. The average values for O_2 consumption were: 80.5 cmm. for liver and 85.6 for kidney of normal rats and 30.3 and 54.5 respectively for rats bearing tumors. A thorough statistical analysis showed that the differences were significant. A decrease in the concentration of the enzyme protein in the

organs of the tumor-bearer is held responsible for this difference.—Z. D.

Lactoflavin und d-Aminosäureoxydase in der Leber tumorkranker Ratten. [Lactoflavin and *d*-Amino Acid Oxidase in the Liver of Tumor-Bearing Rats.] Westphal, U., and Lang, K. [Inst. f. Physiol. und Wehrchem. d. Militärärstl. Akad., Berlin, Germany] *Ztschr. f. physiol. Chem.*, **276**:205-213. 1942.

Since the decrease in *d*-amino oxidase activity in the liver and kidney of animals with Walker carcinoma might be due to a decrease in the content of lactoflavin in these organs, the concentration of this compound in livers of normal and tumor-bearing rats was determined. The lactoflavin was extracted from the minced organ with 80% acetone; the acetone solution was extracted with petrolether; the petrolether, with water. The concentration of lactoflavin in the water solution was measured by the lumiflavin method of Warburg and Christian. The extraction method was tested on pure lactoflavin solutions.

No significant difference between normal liver and that from tumor-bearing rats was found.—Z. D.

Über die d-Aminosäureoxydase in Leberextrakten normaller erwachsner, tumortragender und junger Ratten. [The *d*-Amino Acid Oxidase in Liver Extracts from Normal Adult, Tumor-Bearing, and Young Rats.] Westphal, U., [Inst. f. Physiol. und Wehrchem., Militärärztl. Akad., Berlin, Germany] *Ztschr. f. physiol. Chem.*, **278**:213-221. 1943.

The technic for manometric assay of *d*-amino acid oxidase was further improved. The amount of this enzyme was about twice as great in the tissue extracts from normal rats as in those prepared from rats bearing the Walker tumor. The enzyme content in extracts from young animals is likewise low.—K. G. S.

Über den Zusammenhang zwischen Walker-Tumorwachstum und verminderter d-Aminosäureoxydase-Wirksamkeit. [The Relation Between Growing Walker Rat Tumors and Diminished *d*-Amino Acid Oxidase Activity.] Westphal, U. [Inst. f. Physiol. und Wehrchem. d. Militärärztl. Akad., Berlin, Germany] *Ztschr. f. physiol. Chem.*, **278**:222-229. 1943.

The author claims to have demonstrated that the *d*-amino acid oxidase activity in liver and kidney extracts from rats bearing the Walker carcinoma is less than that in the corresponding extracts from rats without tumors. When the tumor is removed completely by operation, the oxidase activity in the liver returns to the normal values within 10 to 12 days following the operation.—K. G. S.

Brenztraubensaüregehalt des Blutes krebskranker Tiere während Zunahme und Rückgang experimenteller Tumoren. [Concentration of Pyruvic Acid in the Blood of Animals During the Growth and Regression of Experimental Tumors.] v. Euler, H., Högberg, B., and Säberg, I. [Vitamin-Inst. of the Univ. Stockholm, Stockholm, Sweden] *Ztschr. f. physiol. Chem.*, **274**:285-290. 1942.

There was an increase of pyruvic acid in the blood of mice with Ehrlich carcinoma and of rats with tumors induced by benzpyrene and methylcholanthrene but no increase in the blood of 4 human patients with carcinoma of the vulva and rectum. Rats with Jensen sarcoma had an elevated level of pyruvic acid in the blood; after operative removal of the sarcoma or after spontaneous regression as well as regression induced by short waves or x-rays, the pyruvic acid level returned to normal. After x-ray treatment this occurred even before any change in the tumor itself could be observed.—Z. D.

Zymohexase im Blutplasma von Tumor tieren. [Zymohexase in the Blood Plasma of Tumor-Bearing Animals] Warburg, O., and Christian, W. [Kaiser Wilhelm Inst. f. Zellphysiol., Berlin-Dahlem, Germany] *Naturwissenschaften*, **30**:731-732. 1942.

Nonhemolytic plasma of rats with Jensen sarcoma contains up to 15 times as much zymohexase and isomerase as does the plasma of normal rats. The concentration of the reducing enzyme of glycolysis is identical in the two kinds of plasma. Only animals with very large tumors show this increase. Pregnant animals show normal values. Narcosis increases strongly the concentration of zymohexase in the plasma of normal animals. Two possible ways of explaining the increase are discussed.—Z. D.

Tumorferment und Muskelferment. [Enzymes from Tumor and from Muscle.] Kubowitz, F., and Ott, P. [Kaiser Wilhelm Inst. f. Zellphysiol., Berlin-Dahlem, Germany] *Naturwissenschaften*, **30**:732. 1942.

The crystallized reducing enzymes of glycolysis from Jensen rat sarcoma and rat muscle show no difference in their properties. The dissociation constant of the pyridinnucleotide protein complex is identical in both enzymes. The catalytic activity of equal amounts of the enzymes is identical. Antiserum from rabbits prepared by injection of muscle protein inhibits the activity of the tumor enzyme to the same extent as it does that of the muscle.—Z. D.

Isolierung und Kristallisation eines Gärungsfermentes aus Tumoren. [Isolation and Crystallization of a Fermentation Enzyme from Tumors.] Kubowitz, F., and Ott, P. [Kaiser Wilhelm-Inst. f. Zellphysiol., Berlin-Dahlem, Germany] *Biochem. Ztschr.*, **314**:94-117. 1943.

The enzyme under investigation was the active protein of lactic dehydrogenase, designated by Warburg and his colleagues as the "reducing enzyme of fermentation" because, under physiological conditions, its action consists chiefly in the reduction of pyruvic acid to lactic acid with the concomitant oxidation of dihydropyridinenucleotide to pyridinenucleotide (coenzyme I or cozymase). The authors succeeded in isolating this protein in the form of its crystalline mercury salt both from the Jensen sarcoma and from normal muscle tissue of rats. The identity of appearance of the crystals, of the catalytic efficiency in the test reaction, and of their immunochemical behavior indicates the identity of the enzymes isolated from tumor and normal tissue. The test for the activity of the protein is conducted spectrophotometrically by utilization of the fact that the reduced coenzyme has a strong absorption band at 334 mμ, which disappears upon oxidation. The isolation of the protein from rat tissue involves the extraction with distilled water, of pieces of frozen tissue, precipitation of the active principle at pH 5.2, elution with sodium chloride solution, fractional precipitation with yeast nucleic acid, removal of the nucleic acid with the aid of protamin (Salmiridinsulfate), precipitation of the protein with acetone, and crystallization as the mercury salt from

ammonia-ammonium sulfate solution. The crystals are strongly birefringent. They are inactive, but the active protein may be regenerated from them by dialysis against HCN in ammonia-ammonium sulfate solution. The free protein may be preserved by drying from the frozen state and storage *in vacuo* over silica gel at 0°C. Yield: 50 mgm. pure protein from 3,000 gm. tumor tissue (300 rats).—K. G. S.

Gärungsfermente im Blutserum von Tumor-Ratten. [Fermentation Enzymes in the Blood Serum of Tumor-Bearing Rats.] Warburg, O., and Christian, W. [Kaiser Wilhelm-Inst. f. Zellphysiol., Berlin-Dahlem, Germany] *Biochem. Ztschr.,* **314**:399-408. 1943.

The object of this investigation was to ascertain whether the serum of tumor-bearing animals contains fermentative enzymes that are absent from the serum of normal animals. The new optical methods, developed by the authors and based on the difference in ultraviolet light absorption between the reduced and the oxidized form of cozymase, have made it possible to determine quantitatively the presence of 11 different fermentation enzymes in samples of serum amounting to only 0.05 to 0.2 cc. per test. In this experiment, the test animals were rats bearing intraperitoneal Jensen sarcoma.

Results: Normal serum contains zymohexase, isomerase, reducing fermentation enzyme, and 2 phosphorylating enzymes. The reducing enzyme (lactic dehydrogenase) and the two phosphorylases are not increased in the serum of tumor-bearing rats. Zymohexase and isomerase are present in considerably increased quantities if the tumors are large. This is not the case in the serum obtained from gravid animals. The increased amounts of zymohexase and isomerase found in the serum of rats with tumor do not seem to derive from the breakdown of tumor tissue but rather from muscle cells. The blood plasma of human tumor patients shows no increase in zymohexase. The observation made by the authors does not, therefore, represent a "tumor test."—K. G. S.

Über die chemische Nature der Blastokoline und ihre Einwirkung auf keimende Samen, Pollenkoerner, Hefen, Bakterien, Epithelgewebe und Fibroblasten. [The Chemical Nature of the Blastokolines and Their Effect on Germinating Seeds, Pollens, Yeasts, Bacteria, Epithelial Tissue and Fibroblasts.] Kuhn, R., Jerchel, D., Moewus, F., Möller, E. F., and Lettré, H. [Kaiser Wilhelm Inst. f. Med. Forschg., Inst. f. Chem., Heidelberg, und Rudolph Virchow-Krankenhaus, Berlin, Germany] *Naturwissenschaften,* **31**:468. 1943.

The name blastokolin has been given by A. Köckemann to an alcohol and ether soluble substance of unknown constitution occurring in ripe fruits and seeds. The authors find that the *d*-sorbin oil, first isolated by A. W. Hofmann from certain berries, as well as several closely related synthetic substances, are highly active in the blastokolin test in which seeds of *Lepidium sativum* are used as test object. Coumarin is still more active. The common feature of the active compounds is that they represent unsaturated lactones, containing 1 or 2 rings. In contrast to chicken heart fibroblasts, Ehrlich carcinoma tissue cultures are not affected in their growth rate by 1 to 12 μgm. per cc. of synthetic or natural sorbin oil.—K. G. S.

The Distribution of Iron and Copper in Malignant Neoplastic Disease. Buchwald, K. W., and Hudson, L. [State Inst. for Study of Malignant Diseases, Buffalo, N. Y.] *Cancer Research,* **4**:645-653. 1944.

Material from 43 autopsies was analyzed for moisture, iron, and copper contents. By an improved method of ashing the loss of metals by volatilization was reduced to a minimum. The moisture content varied little. The iron content calculated on the basis of dry weight places the material in the following groups in decreasing order: high, spleen, liver, and lung; intermediate, kidney, heart, and tumor; low, pancreas, rib, thyroid, and bile. The copper content calculated on the basis of dry weight places the material in the following groups in decreasing order: high, bile and liver; intermediate, kidney, heart, and pancreas; low, lung, tumor, spleen, thyroid, and rib. Except for bile, tumor had the highest percentage of moisture (83.9 ± 0.47). Tumor had an iron content of 25.6 ± 3.02 mgm. Fe per 100 gm. dry tissue and a copper content of 0.84 ± 0.063 mgm. Cu per 100 gm. dry tissue. The anemia often developing in malignant neoplastic disease is not produced by a lack of iron or copper. Livers showing fatty degeneration had low moisture contents. In fibrosis of the liver the copper increased. The iron and copper in the heart decreased in brown atrophy and fragmentation of the muscle. In fragmentation of the heart muscle the moisture content was lowered.—Authors' abstract.

Über den Einfluss der Keimdrüsenwirkstoffe auf Entstehung und Wachstum maligner Tumoren. [Influence of Sex Hormones on the Formation and Growth of Malignant Tumors.] Hackmann, C. [Inst. f. exper. Path. der I. G. Farbenind. A.-G., Elberfeld, Germany] *Ztschr. f. physiol. Chem.,* **274**:31-38. 1942.

1. The influence of diethylstilbestrol (Cyren A) on the Ehrlich mouse carcinoma was investigated. The hormone was injected subcutaneously twice a week for 3 to 4 weeks, as a suspension in isotonic NaCl the total dose being 3 to 6 mgm. Four groups of 10 mice each were used with an equal number as controls. No significant influence on the growth of the tumor could be observed.

2. In a second series of experiments the influence of castration on the frequency of recurrences after operative removal of spontaneous mammary carcinoma in mice was investigated. An inbred strain with 45% tumor incidence was used. Tumors appeared in the 10th to 12th month of life, and were removed when reaching a diameter of 5 to 10 mm. One hundred and fifty mice were operated upon, and 36 of them simultaneously castrated. Fifty-three mice (14 castrated) died without tumor in less than 2 months after operation. Of the survivors 19 (6 castrated) never developed any tumors. No significant difference between the castrated and noncastrated groups could be observed.—Z. D.

Excretion of Neutral 17-Ketosteroids in Adrenal Cortical Tumor and Feminine Pseudohermaphroditism with Adrenal Cortical Hyperplasia. Engstrom, W. W., Mason, H. L., and Kepler, E. J. [Mayo Foundation, and Mayo Clinic, Rochester, Minn.] *J. Clin. Endocrinol.,* **4**:152-155. 1944.

The range in average excretion of neutral 17-ketosteroids in the urine of 8 patients with adrenal cortical tumors, the diagnosis of which was established by operation, was

from 2.8 to 857 mgm. per 24 hours. In 3 patients with female pseudohermaphroditism, in whom the authors thought that hyperplasia of the adrenal cortex probably was present, the daily values were 13.5, 37.0, and 75.12 mgm. Separate measurements of α and β fractions of the 17-ketosteroids are not reported at this time.—J. B. H.

The Effect of Castration, Theelin, and Testosterone on the Incidence of Leukemia in a Rockefeller Institute Strain of Mice. MURPHY, J. B. [Rockefeller Inst. for Med. Research, New York, N. Y.] *Cancer Research,* **4**:622-624. 1944.

The spontaneous leukemia rate in the females of the Rockefeller Institute Leukemia strain of mice is consistently higher than in males. In the present experiments the incidence in ovariectomized females was 90.3%, in intact females 88.4%, and in castrated males 97%. These figures are significantly different from the incidence in intact males, 53.5%, and in ovariectomized females treated with testosterone propionate, with a rate of 58.3%. On the basis of these findings it is suggested that the sex difference in susceptibility in the mouse strain under observation is due to an inhibitory effect of the male sex hormone rather than to a stimulation of the ovarian secretion.

So many of the castrated males treated with theelin died before or in the early leukemia age period that not a sufficient number were left to give significant figures on the leukemia incidence in this group.—Author's summary.

Ein Papillom-Virus aus Kaninchenhaut. [A Papilloma Virus from Rabbit Skin.] DANNEEL, R. [Arbeitsstaette f. Virusforschg. d. Kaiser Wilhelm-Inst. f. Biochem. u. Biol., Berlin-Dahlem, Germany] *Naturwissenschaften,* **29**:364-365. 1941.

Four out of 5 cell-free extracts obtained from the skin of apparently normal domestic rabbits, when rubbed into the skin of similar animals after superficial scarification with sand paper, induced the formation of papillomas that were very similar to Shope's cottontail rabbit papillomas and that shared with these the property of being transferable to other domestic rabbits by cell-free extracts. An auto-infection experiment in which a rabbit was inoculated with an extract from its own skin was successful. The author believes that accidental infection of the animals by contact with virus-carrying rabbits is ruled out. As long as there is no proof of the identity of the "normal skin" virus with the Shope papilloma virus, he feels there is a possibility that all papillomas thus far observed in domestic rabbits and their tendency to change into carcinomas may have to be attributed to the action of the "normal skin virus."—K. G. S.

Bemerkung zu meiner Mitteilung: Ein Papillom Virus aus Kaninchenhaut. [Addendum to previous article: A Papilloma Virus from Rabbit Skin.] DANNEEL, R. [Kaiser Wilhelm.-Inst. f. Biochem. u. Biol., Berlin-Dahlem, Germany] *Naturwissenschaften,* **31**:551. 1943.

The experiments on the production of skin papillomas by means of extracts from normal rabbit skin, reported by the author in *Naturwissenschaften,* **29**:364-365. 1941, and in *Biol. Zentr.,* **61**:445, 1941, were not reproducible.—K. D.

Antigene und bösartige Geschwülste (III). [Antigens and Malignant Tumors (III).] MICHEEL, F., and EMDE, H. [Univ. Münster, Münster i. W., Germany] *Ztschr. f. physiol. Chem.,* **269**:217-226. 1941.

In extension of previous experiments (Micheel, F., and Emde H., *ibid.,* **266**:249. 1940; *Z. angew. Chem.,* **54**:293. 1941) the prevention of benzpyrene sarcomas in mice by the administration of certain antigens was studied in a total of 600 animals. The antigens tested included crystalline horse serum albumin, freed from inorganic ions by electrodialysis, crystalline and electrodialyzed ovalbumin, snake venom (Indian cobra, *Naja tripudans*), a high-molecular, almost non-toxic fraction of this venom, and commercial gelatin ("emulsionsgelatine," Oswald, Hofheim Co., Taunus). Fifteen to 30 γ of the antigens were injected twice or once weekly for various periods.

The most effective antigen was the highly purified horse serum albumin. In one experiment only 44% of 77 mice had sarcoma compared with almost 90% among 77 controls. The ovalbumin was less active; gelatin showed a small, positive effect. The snake venom and several of its fractions had a marked effect, but its evaluation was made difficult by the high toxicity. Mice treated with benzpyrene exhibit an increased sensitivity to snake venom as compared with normal mice.—K. G. S.

Antigene und bösartige Geschwülste. IV. [Antigens and Malignant Tumors. IV.] MICHEEL, F., and EMDE, J. [Univ. Münster, Münster i. W., Germany] *Ztschr. f. physiol. Chem.,* **275**:215-216. 1942.

Mice that normally developed tumors when injected with 1 mgm. of benzpyrene suspended in olive oil did not show any tumor formation when accidental skin infections occurred. This observation was made on 13 animals that, out of 20, survived the treatment with benzpyrene for 158 days. The incidence in uninfected mice at this time was 76%. The relation of this phenomenon to the reported influence of infectious diseases on cancer development in human beings is discussed.—Z. D.

Antigene und bösartige Geschwülste. V. [Antigens and Malignant Tumors. V.] MICHEEL, F., EMDE, H., and DÖRNER, H. [Univ. Münster, Münster i. W., Germany] *Ztschr. f. physiol. Chem.,* **275**:258-266. 1942.

In previous experiments of the authors it was observed that injections of an antigen-like horse serum albumin into mice treated with benzpyrene (1 mgm. suspended in olive oil) lowered the normal incidence of tumors from 70% to 30%. Gelatin had no such effect. To determine whether this inhibitory influence was due to the antigenic character of the protein, these experiments were repeated with insulin and with an antigenic derivative of gelatin. This derivative was prepared by coupling gelatin with an azide of the β-glucosido-N-carbobenzoxy-*l*-tyrosine. Insulin (inactivated, before being injected, by reduction according to the method of du Vigneaud) had no influence. The gelatin antigen decreased the incidence to 50%. The antigen dose was 15 γ injected twice a week from 8 to 14 days before the administration of benzpyrene until 90 days after the beginning of the carcinogen treatment. Thereafter, one injection a week was given.

Water extracts of tumors induced by benzpyrene in mice

also had a depressing effect on tumor incidence after benzpyrene treatment. This is also correlated to their antigenic property in the host.—Z. D.

Experiments on the Inhibitor Occurring in Rous No. 1 Sarcomas. CARR, J. G. [Inst. of Animal Genetics, Edinburgh, Scotland] *Brit. J. Exper. Path.*, **25**:56-62. 1944.

Recurring Rous tumors (which had previously been found to yield noninfective filtrates), and tumors that were nonfilterable by virtue of their slow growth, were shown to contain a quantity of "inhibitor", as judged from the neutralization of Rous agent by their extracts. Serum antibody to the Rous No. 1 virus was always associated with the presence of inhibitor, and is considered to be identical with it. The antibody causes a reduction in the amount of virus obtained from tumor extracts by forming floccules of virus and antibody and by neutralization of virus remaining in suspension. The amount of antibody contained in a tumor growing in an immune bird is sufficient to inactivate all the virus that could be extracted from the tumor cells.—A. H.

Transplantable Methylcholanthrene Skin Carcinomas of Mice. COOPER, Z. K., FIRMINGER, H. I., and RELLER, H. C. [Barnard Free Skin and Cancer Hosp., and Washington Univ. Sch. of Med., St. Louis, Mo.] *Cancer Research*, **4**:617-621. 1944.

Three lines of transplantable methylcholanthrene skin carcinomas of mice have been established. Tumor I, originally a well differentiated, keratinizing, squamous cell carcinoma, has been carried through 21 subcutaneous passages over a period of 2½ years. During passage its microscopic appearance has changed, and it is now an undifferentiated, nonkeratinizing, squamous cell carcinoma. The average percentage of successful inoculations is 68.5, the highest for the 3 lines.

Tumor II has been carried through 20 subcutaneous passages. It is a highly differentiated, keratinizing, squamous cell carcinoma whose microscopic appearance has not undergone any significant change. It grows somewhat more slowly and has a lower percentage of successful inoculations (39.3) than tumor I.

Tumor III was carried through 15 subcutaneous passages and then was lost. It was originally more differentiated and showed less tendency to keratinize than either tumor I or tumor II. Like tumor II, its microscopic appearance remained relatively unchanged. The average percentage of successful inoculations (66.2) was higher than that of tumor II, but almost the same as that for tumor I.—Authors' summary.

Zytoplasmatische Nukleotide in Tumorzellen. [Cytoplasmic Nucleotides in Tumor Cells.] CASPERSSON, T., NYSTRÖM, C., and SANTESSON, L. [Roy. Gustav. V. Jubilee Clinic, Stockholm, Sweden] *Naturwissenschaften*, **29**:29-30. 1941.

Caspersson's technic for measuring the ultraviolet absorption spectrum of individual cellular components (*Skand. Arch. Physiol.*, **73**:Supplement 8. 1936) was employed in preliminary examinations of human carcinoma of various organs (colon, stomach, breast). It was found that the cytoplasm of the cells observed contained a considerably higher concentration of materials having an absorption maximum at 2,600 A., which is characteristic for nucleotide groups, than do the corresponding cells of normal tissues. The amount of these nucleotides seems to run parallel to the rate of proliferation of the tissues examined. Inasmuch as the nuclear reaction (Feulgen test) is negative in all instances, it is concluded that at least the main portion of these nucleotides belongs to the ribose rather than the desoxyribose type. The high nucleotide concentration is correlated with protein synthesis which, as in normal cells, is accomplished with the participation of the nucleoli and the cytoplasmic nucleotides as well as of basic proteins of the histone type.—K. G. S.

Zur Teilungsgeschwindigkeit der Zellen des Mäuse-Ascites-Tumors. [The Rate of Cell Division of the Mouse Ascites Tumor.] LETTRÉ, H. [Allg. Chem. Univ. Lab., Göttingen, Germany] *Naturwissenschaften*, **31**:467-468. 1943.

The first part of the paper is devoted to a statistical consideration of the evaluation of ascites tumor experiments. The second more extensive part consists in the application of the colchicine technic to the problem. Small doses of colchicine (1 to 50 μgm.) were injected into the animals, and samples of ascitic fluid were withdrawn at different times in order to count the mitotic figures in the cells. It was assumed that colchicine does not stimulate cell division but merely arrests mitosis. Small doses of the drug failed to stop all of the mitoses, while too large doses interfered with the beginning of the mitotic process. It is concluded from the measurements that the cell of the ascites tumor requires a little longer than 1 day to maturate to the stage of mitosis, and that it will divide subsequently into 2 new cells within 15 minutes. Analogous data for normal tissues are not yet available.—K. G. S.

Decreased Mutual Adhesiveness, A Property of Cells from Squamous Cell Carcinomas. COMAN, D. R. [Univ. of Pennsylvania Med. Sch., Philadelphia, Pa.] *Cancer Research*, **4**:625-629. 1944.

The mutual adhesiveness of normal and of neoplastic squamous epithelial cells from the lip and from the cervix uteri was measured in milligrams by a method dependent upon the bend produced in a microneedle when a pair of cells was pulled apart. Normal squamous epithelial cells from the lip and from the cervix were found to have relatively high values of adhesiveness. Benign neoplastic squamous cells from skin papillomas had values of adhesiveness in the same range as did normal squamous cells. Malignant neoplastic squamous cells from carcinomas of the lip and of the cervix showed mean values of adhesiveness far below that of the normal cells. Decrease in mutual adhesiveness in cells from carcinoma of the lip and cervix uteri may constitute the physical basis for the malignancy of these cells. Such cells, no longer strongly adherent to each other in sheets, would presumably break loose and thus be free to penetrate tissue spaces and vessels. Local invasiveness and distant metastasis would thus be promoted. It is suggested that decreased mutual adhesiveness in cells of squamous cell carcinoma may be related to a lowered calcium content of these cells.—Author's abstract.

The Effect of Parenteral Injection of Synthetic Amino Acids upon the Appearance, Growth and Disappearance of the Emge Sarcoma in Rats. Beard H. H. [Louisiana State Univ., Sch. of Med., New Orleans, La.] *Arch. Biochem.*, **1**:177-186. 1942-43.

A solution of certain pure amino acids was administered to young rats bearing the Emge sarcoma. Daily parenteral injection around the tumor or even ingestion of the amino acid solution, when begun shortly after the transplants were made, caused at least 60% of the tumors to disappear, whereas the tumors in control animals did not disappear. Retransplantation in the animals from which the tumors had disappeared resulted in a low percentage of takes, and the majority of the tumors that did grow, later disappeared spontaneously. Theories are presented to explain the results.—H. J. C.

Über Leberveränderungen nach Verfütterung von bösartigen Tumoren. [Liver Changes after Ingestion of Malignant Tumors.] Rodewald, W., and Klein, H. [Allg. Inst. gegen die Geschwulstkrankh. u. Pathol. Inst., Berlin, Germany] *Naturwissenschaften*, **31**:277-278. 1943.

Pure bred mice were fed 0.5 to 1 gm. of tumor tissue. A relatively high mortality occurred after the first 48 hours. After ingestion of mouse mammary adenoma, degenerative liver changes were found within 4 to 10 hours. When human breast carcinoma was fed, maximum liver changes were found after 14 hours. The histological picture appeared to be that of acute liver damage. Several kinds of tissue have been used, but the liver damage has been observed only after ingestion of malignant tumors.—K. D.

Alloxan in the Treatment of Insulin Producing Islet Cell Carcinoma of Pancreas. Brunschwig, A., Allen, J. G., Owens, F. M., Jr., and Thornton, T. F., Jr. [Univ. of Chicago, Chicago, Ill.] *J. A. M. A.*, **124**:212-216. 1944.

Alloxan, the ureide of mesoxalic acid, also a component of the uric acid molecule, has been observed to produce specific necrosis of the islets of Langerhans in the rabbit and dog with resultant hyperglycemia. Similar histologic effects were not observed in man receiving larger doses. Alloxan was administered as a chemotherapeutic agent to a patient with insulin-producing islet cell carcinoma metastatic to the liver, who presented recurring attacks of hyperinsulinism increasing in frequency and severity. Temporary symptomatic relief, in that attacks were obviated for brief periods, followed each series of injections. Death resulted from a complication at laparotomy. Alloxan did not cause necrosis of the malignant islet cells.—M. E. H.

Chemical Treatment of Tumors. IX. Reactions of Mice with Primary Subcutaneous Tumors to Injection of a Hemorrhage-Producing Bacterial Polysaccharide. Shear, M. J., and Perrault, A. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:461-476. 1944.

A polysaccharide fraction was obtained from culture filtrate of *Serratia marcescens* (*Bacillus prodigiosus*). This polysaccharide fraction when injected in doses containing a fraction of a microgram produced hemorrhage in mice bearing primary subcutaneous tumors induced by injection of a marginal dose of 3,4-benzpyrene. It was found that for mice bearing primary subcutaneous tumors the L.D.50 was about 15 mgm., while for normal control mice the L.D.50 was about 100 mgm. However, the tolerance both in the tumor-bearing and the control mice was increased about 13 to 16 times if the animals were first given a small dose and then progressively increasing doses. The amount of hemorrhage was dependent upon the dose and size of the tumors. The larger the dose the more severe the hemorrhage and the greater the proportion of affected tissue in the tumor. Also it was shown that with a given dose, the larger the tumor the more severe and extensive was the hemorrhage. When extensive hemorrhage occurred, the animal usually died within 1 or 2 days. The areas of the tumor that were unaffected by the initial dose were often resistant to the action of subsequent doses. It would seem that some sort of immunity may have been developed following the first injection. The authors discuss some relevant clinical literature.—D. S.

Das Wesen der krebsigen Umwandlung der Zelle und die Ausblicke einer biologischen Krebstherapie. [The Nature of the Malignant Change and the Prospects for a Biological Treatment.] Rondoni, P. [Milan, Italy] *Schweiz. med. Wchnschr.*, **72**:1185-1187. 1942.

Any one of a multitude of external agents may elicit the malignant change, which is irreversible and inherited by the daughter cells. Thus a new cell race emerges, and the view that this is a result of somatic mutation is widely prevalent.

Despite its great proliferative energy the malignant cell is not especially hardy. On the contrary, it is a rather delicate cell. Its preference for glycolysis rather than respiration is not specific, and probably is not concerned in the initiation of the malignant transformation, but seems to be rather the result of adaptation to a lower vital plane.

Many observations suggest as the cause a denaturization of some of the cell's proteins, which thereupon become alien and behave somewhat as an endogenous virus. Some such intracellular change appears to be the immediate cause of cancer, all external agents being but contributing causes.

If malignancy is the result of a specific biochemical alteration the discovery of an appropriate immunotherapy need not be despaired of.—W. H. W.

Progress in Cancer Research. I. Animal Experimentation in the Solution of the Cancer Problems. Selle, W. A. [Univ. of Texas, Sch. of Med., Galveston, Texas] *Texas State J. Med.*, **40**:52-56. 1944.

A review.—J. L. M.

Clinical and Pathological Reports

Ueber "Präcancerosen?" und Probeexzisionen. ["Precancerous?" Conditions and Biopsy.] Obern-dorfer, S. [Univ. Istanbul, Istanbul, Turkey] *Schweiz. med. Wchnschr.*, **72**:1187-1189. 1942.

Since the malignant change, widely regarded as a mutation, is a fortuitous and rare event that cannot be foreseen, hardly any tissue change is an invariable antecedent of cancer. The word "precancerous" is much too commonly used, and should be limited strictly to such lesions, of which there are only two in man—xeroderma pigmentosum and familial, diffuse, intestinal polyposis.

Other lesions, such as hyperkeratosis, leukoplakia, gastric ulcer, cholecystitis with stones, moles, and so on, may terminate in cancer but do not necessarily do so. It is especially unjustifiable to call mastopathia cystica precancerous, for the author has seen cancer arise rather more often in an apparently normal breast than in one that was involved by the so-called chronic mastitis.

Doubtful lesions should be removed, in whole or in part, and submitted to a pathologist of the widest possible experience, who should under no circumstances delegate his enormous responsibility to an inexperienced assistant.

Except in the case of moles of the skin, where biopsy is absolutely contraindicated, there is practically no danger that removal of part of a tumor will be followed by its dissemination or by stimulation of its growth energy. Clinical and pathological experience, and animal experiments, all confirm this statement.

Against the barely imaginable danger of removing part of a tumor for examination should be weighed the great advantage of certain diagnosis and the prevention of unnecessarily extensive operation later on. The author has seen too many amputations of the breast and extirpations of the uterus where minute examination of the organs removed showed that these mutilating operations had been unnecessary and could have been avoided by a preceding biopsy.—W. H. W.

Frequency and Course of Cancer in Diabetics. Ellinger, F., and Landsman, H. [Montefiore Hosp., New York, N. Y.] *New York State J. Med.*, **44**:259-265. 1944.

During the years 1933 to 1941 a total of 1,280 patients has been recorded at Montefiore Hospital for Chronic Diseases as suffering from diabetes mellitus. Of these, 39 or 3.04% had malignant tumors. This cancer incidence is in agreement with that of 2.95% of 14,332 cases of diabetes collected from the world literature. Since the cancer incidence in a general population (state of New York in 1941) was 0.46%, that means a definitely higher cancer incidence in diabetics. Of the 39 patients, 33 died, 2 from causes other than cancer, 4 patients are still alive, and in 2 cases there was no follow-up.

In agreement with previous observations, a more virulent course of malignant growth was found with increasing severity of the diabetic condition. The average lifetime after onset of tumor symptoms in the series presented in this paper decreased from 4.6 years in mild diabetes to 0.9 year in severe diabetes. Nine of the 39 patients with cancer and diabetes lived for 5 years and longer after onset of tumor symptoms. All but 1 of these cases belonged to the group with mild diabetes.—J. L. M.

Cervical Lymph Node Metastasis as the First Symptom of Cancer. Martin, H., and Morfit, H. M. [Memorial Hosp., New York, N. Y.] *Surg., Gynec., & Obst.*, **78**:133-159. 1944.

Clinical discussion with reports of 6 illustrative cases.—J. G. K.

Heredity

Carcinoma Corporis Uteri in Two Sisters Aged 34 and 32 Years. Purdie, A. W. *Proc. Roy. Soc. Med.*, **37**: 426. 1944.

Two sisters aged 34 and 32 underwent hysterectomy for endometrial carcinoma, while a third sister underwent hysterectomy "for a benign condition." Their mother died of carcinoma of the rectum at 68. The author remarks of cancer of the endometrium that "it is surprising how many observers find the average age within the narrow limits of 56 to 58 years."—E. L. K.

Adenocarcinoma of the Small Intestine in Father and Daughter. Foster, D. B. E. [Llandough Hosp., Cardiff, Wales] *Brit. M. J.*, **2**:78-79. 1944.

The father, aged 43, had attacks of abdominal pain and a positive occult blood test. An operation for obstruction showed an intussusception due to a jejunal tumor. This was an adenomatous polyp "showing disorderliness suggestive of adenocarcinomatous transformation." The daughter, aged 16, showed at operation for an acute abdominal condition a similar intussusception in the ileum, due to a polyp containing an area of adenocarcinoma. Both patients, and the father's brother, "presented a diffuse brownish pigmentation of the lips and face"; the brother had had attacks of acute abdominal pain with passage of blood.—E. L. K.

Radiation—Diagnosis and Therapy

X-ray Diagnosis of Bronchogenic Carcinoma. Scatchard, G. N. [Meyer Memorial Hosp., Buffalo, N. Y.] *New York State J. Med.*, **44**:617-620. 1944.

A general discussion. The author points out that the x-ray can demonstrate most early bronchiogenic carcinomas if the condition is kept in mind and searched for. If immediate bronchoscopy is done in all suspicious cases, and if exploratory thoracotomy, performed early as a diagnostic procedure, is followed by a pneumonectomy in operable cases, the mortality rate from bronchiogenic carcinoma can be lowered. X-ray therapy is of great palliative value but should not be used until the lesion is proved to be inoperable.—J. L. M.

The Fluoroscopic Signs of Posterior-Wall Tumors of the Stomach, Especially those Signs Developed by Palpatory Pressure. A Study. Jonas, S. [New York, N. Y.] *Rev. Gastroenterol.*, **11**:27-36. 1944.

The methods that may be employed for fluoroscopic detection of posterior-wall tumor include observation of the filling process and of the peristalsis of the curvatures as

well as palpatory pressure exercised during gastric filling and upon the filled stomach. The author discusses the fluoroscopic signs of posterior-wall tumors.—M. E. H.

Roentgenologic Diagnosis of Carcinoma of the Colon. Baird, L. W. [Scott and White Clinic, Temple, Tex.] *Texas State J. Med.* **39**:243-246. 1943.

The author emphasizes the value and importance of the roentgenologic examination in tumefactive lesions of the colon. The limitations of the examination in the presence of infection are described.

One hundred consecutive tumefactive lesions of the colon observed roentgenologically at the Scott and White Clinic in the last 4 years are reviewed. Of these, 86 were primary carcinomas, 10 were inflammatory granulomas, and 4 were malignant lesions of the abdomen and pelvis secondarily involving the colon. Of the 86 primary carcinomas of the colon, the roentgenologic characteristics of carcinoma were visualized so that a definite diagnosis of carcinoma was made in 76. Of these 76 carcinomas, 19 were perforated, and 13 were completely obstructive. In the remaining 10 carcinomas the roentgenologic characteristics were not definitely elicited. Six were of the ileocecal region complicated by perforation and abscess formation. Of the 26 perforated carcinomas with inflammatory manifestations, the malignant disease had remained sufficiently localized to justify extirpation of the growth in only 7 instances, while in the remaining 60 nonperforated carcinomas, extirpation was possible in 41.—J. L.M.

Diagnostic and Therapeutic Value of X-Ray in Carcinoma of the Colon. Koenig, E. C., and Culver, G. J. [Buffalo General Hosp., Buffalo, N. Y.] *New York State J. Med.*, **43**:1723-1727. 1943.

The important features of roentgen diagnosis of carcinoma of the colon are listed. Except in selected cases, surgery rather than irradiation is strongly advised.—J. L. M.

Abdominal Tumors of Questionable Origin: Roentgenological Aspects. Hartung, A. [Chicago, Ill.] *Illinois M. J.*, **86**:14-16. 1944.

Roentgen examinations are of definite value for ascertaining the nature or origin of practically all tumorous masses of questionable origin in the abdomen. The closest cooperation between the clinician and roentgenologist is needed to interpret the symptoms, signs, and laboratory findings, not only to arrive at a correct diagnosis but also to determine prognosis and therapy.—M. E. H.

Wann is die Röntgentherapie des Krebses indiziert und was ist von ihr zu erwarten? [When is Roentgentherapy Indicated in Cancer and What is to be Expected of It?] Lüden, M. *Schweiz. med. Wchnschr.*, **72**:1237-1242. 1942.

The first half of the question is answered by the statement that roentgentherapy is always indicated for inoperable neoplasms. All operable cancers, with the exception of those of the skin, must be treated by surgery.

As for the second half, statistics from several countries suggest that by and large, about 12% of permanent cures may be expected.

The author enthusiastically recommends postoperative raying, particularly for cancer of the breast, and closes with a short discussion of the results of roentgentherapy for tumors at different sites.—W. H. W.

Radium in Present-Day Therapeusis. Quick, D. [New York, N. Y.] *New York State J. Med.*, **44**:981-985. 1944.

A general discussion. The author believes that at present radium is not being used to the full extent of its proved value in the treatment of malignant neoplastic diseases.—J. L. M.

Epithelioma of the Cheek Developing 15 years After Tricho X-Ray Treatment for Hair on the Face. Kaplan, I. I. [New York, N. Y.] *New York State J. Med.*, **43**:1758-1759. 1943.

Radiation therapy when too often repeated and improperly employed may cause untoward damage to the skin. Destructive changes or malignant transformation may occur even after several years have elapsed. X-ray therapy for cosmetic epilation of superfluous hair is fraught with danger and should not be used. In the case reported, epithelioma occurred 15 years after excessive repeated doses of unfiltered x-rays had been administered by the Tricho system for removal of superfluous hair on the face.—J. L. M.

Concentration Method of Radiotherapy for Cancer of the Mouth, Pharynx and Larynx. Cutler, M. [Chicago Tumor Inst., Chicago, Ill., and Hines Veterans Hosp., Hines, Ill.] *Am. J. Roentgenol.*, **51**:739-746. 1944.

Two hundred and ninety patients with cancer of mouth, pharynx, and larynx were divided into 5 groups and treated by different technics—one by means of radium, the others by different types of x-ray series. Each technic is presented in detail, with one case report and comments. The conclusion is reached that a so-called "concentration method" of large daily doses over a treatment period of 10 to 18 days is most valuable. By this method, the results in radioresistant forms of cancer, particularly those in the larynx, have been definitely improved. A radiotherapeutic test is offered for borderline cases in which the decision must be made between radiotherapy and laryngectomy.—E. H. Q.

Concentration Radiotherapy of Cancer of the Larynx. A Study of 413 Cases. Cutler, M. [Chicago Tumor Inst., Chicago, and Hines Veterans Facility, Hines, Ill.] *J. A. M. A.*, **124**:967-976. 1944.

Concentration radiotherapy has proved to be the most effective form of irradiation for intrinsic squamous carcinoma of the larynx. The percentage of cures is dependent on the extent of the lesion and the efficiency of the treatment. The most significant result of this research is the eradication, by means of an improved method of radiotherapy, of a group of intrinsic squamous carcinomas of the larynx, so advanced as to have required total laryngectomy and hitherto generally regarded as radioresistant and incurable by irradiation.—M. E. H.

Treatment of Cancer of the Larynx by Roentgen Irradiation. Blady, J. V., and Chamberlain, W. E. [Temple Univ. Hosp., Philadelphia, Pa.] *Am. J. Roentgenol.*, **51**:481-495. 1944.

Of 36 cases of cancer of the larynx treated by irradiation between 1931 and 1937, the lesions were intrinsic

in 64%, and extrinsic in 36%. Intrinsic cancer is predominantly squamous cell grade II, extrinsic usually grade III or IV. The first is radiosensitive when limited to the intrinsic larynx. All were treated with 180 kv. x-rays filtered by 2.0 mm. Cu. Details of dosage technic and tumor doses delivered are given. Complications of radiation treatment included skin and mucous membrane reaction, dyspnea, dysphagia, and (rarely) radionecrosis. Of the 23 patients with intrinsic cancer, 13 have been free of disease 5 years or more; 9 died of the disease, 1 died of other causes with no evidence of cancer. Of the 13 patients with extrinsic cancer, 9 died of the disease, 3 have been well for 5 years or more. In the group with intrinsic cancer 4 patients had recurrences; 2 of these are alive and with no evidence of disease following further radiation therapy. Of the 9 who died with extrinsic cancer, 6 had metastases on admission.—E. H. Q.

Some Experiences in the Treatment of Bronchial Cancer. MATTICK, W. L. [State Inst. for Study of Malignant Diseases, Buffalo, N. Y.] *Am. J. Roentgenol.*, **52**:24-30. 1944.

Detailed reports are given of 4 cases of bronchial cancer, histologically proved, treated by x-ray therapy with good results.—E. H. Q.

Roentgen Rays in the Treatment of Carcinoma of the Bronchus. With an Analysis of 69 Cases Treated in the State of Wisconsin General Hospital from 1933 to 1943. POHLE, E. A., and SIRIS, E. L. [Wisconsin General Hosp., Madison, Wis.] *J. Thor. Surg.*, **13**:67-83. 1944.

This is an analysis of 69 cases treated in the Wisconsin General Hospital from 1933 to 1943. The majority of the tumors were of the squamous cell variety. Few patients survived for 5 years, but weight gain and a transient sense of well-being resulted from radiation therapy given in 2 series 3 months apart. Three patients are described in detail.—E. E. S.

Supervoltage Therapy of Esophageal Carcinoma. BUSCHKE, F., and CANTRIL, S. [Swedish Hosp., Seattle, Wash.] *Radiology*, **42**:480-492. 1944.

A study of results of treatment of thoracic esophageal carcinoma indicates that 200 kv. therapy is only palliative and that some other type of treatment is to be sought for curative measures. The authors' experience with 800 kv. therapy includes only 5 cases in the past 4½ years. No end results can be reported as yet, but a discussion of treatment is given. Greater depth doses can be administered with the higher voltage than with 200 kv., the treatment is better withstood by the patient, and it is hoped that end results will improve. No patient is treated if there is metastasis or if there is not a reasonable hope of palliation or cure.—R. E. S.

Roentgen Therapy of Wilms' Tumor. ROWE, E. W., and FRAZER, M. D. [Lincoln, Neb.] *Radiology*, **42**:107-116. 1944.

Four cases of Wilms' tumor are presented, 1 of which was treated by surgery and postoperative radiation, while the remaining 3 had preoperative irradiation, nephrectomy, and postoperative irradiation. The first patient died after 7 months, while the remaining 3 are living 4 years and 9 months, 2 years, and 7 months after treatment. The authors therefore recommend preoperative and postoperative irradiation, with operation in 4 to 6 weeks following the first series.—R. E. S.

Carcinoma of the Cervix Complicated by Complete Procidentia: Radiation Therapy. HARVEY, R. A., and RITCHIE, R. H. [Univ. of Rochester Sch. of Med., and Strong Memorial Hosp., Rochester, N. Y.] *Radiology*, **41**:48-51. 1943.

Seventy-eight instances of carcinoma of the cervix occurring in cases of procidentia were found in the literature, an incidence of about 0.14%. A case is added that occurred in an 81 year old woman treated first by external radiation followed by radium. A depth dose of 4,686 r was delivered in 26 days to the mid-cervix, and a total dose of 3,500 mgm./hr. of radium was added. The procidentia was completely relieved, and the patient is free of disease 14 months later.—R. E. S.

Fracture of the Neck of the Femur Following Irradiation for Carcinoma of the Uterus. CONZETT, D. C. [Fort Riley, Kans.] *J. Iowa M. Soc.*, **33**:15-17. 1943.

A case report with discussion.—J. L. M.

X-Ray Treatment of Bone Tumors. MARTIN, C. L. [Dallas, Tex.] *Texas State J. Med.*, **39**:285-288. 1943.

A brief discussion. Four case histories are presented.—J. L. M.

Treatment of Osteogenic Sarcoma with Preoperative Roentgen Radiation in Large Doses. MCNATTIN, R. F. [Cook County Hosp., Chicago, Ill.] *Radiology*, **42**:246-248. 1944.

The treatment of osteogenic sarcoma is far from satisfactory in the majority of cases. In an attempt to improve results, preoperative irradiation has been tried, multiple ports and large total doses to the point of radiation necrosis being used. The delay in amputation does not increase the likelihood of metastasis. Preliminary studies are encouraging, though end results are not yet available.—R. E. S.

The Value of Roentgen Therapy in Carcinomatous Metastases to Bone. KOENIG, E. C., and CULVER, G. J. [Buffalo General Hosp., Buffalo, N. Y.] *Radiology*, **41**:38-41. 1943.

Three theories concerning the way radiation acts on metastasis are as follows: (1) by action on the associated nonspecific inflammatory reaction, (2) action on the malignant process itself, or (3) a non-identified action on nerves. Diminution of symptoms following x-ray may come on within 5 days, although relief usually takes somewhat longer. Apparently the first effects are nonspecific, and later there is an effect on the tumor cells themselves. There are two types of patients with metastasis. In one group are those who are debilitated and cachectic and as a rule are not eligible for x-ray treatment since it only increases the discomfort of their last days. Those in the second group, in whom the primary symptom is pain, should be given roentgen therapy since it may be followed by regression of disease, alleviation of pain, improvement of the general condition, and prolongation of life.—R. E. S.

Osseous Metastases from Graded Cancers of the Breast. With Particular Reference to Roentgen Treatment. Burch, H. A. [Elmira, N. Y.] *Am. J. Roentgenol.*, **52**:1-23. 1944.

Of a group of 200 patients treated at the Mayo Clinic from 1925 to 1934, 41 with spinal or pelvic metastases had complete histological, clinical, and roentgenographic studies. Analysis of these 41 cases showed that bone metastases appeared earlier the higher the grade of malignancy of the tumor, the younger the patient, and the greater the degree of axillary metastasis found at operation. Grade of malignancy had no relation to location or number of metastases, roentgenographic appearance of bone lesions, or recalcification following x-ray treatment. The time elapsing between onset of bone symptoms and beginning of treatment was important; 35 of 38 patients coming to treatment within 10 months obtained relief in some degree, those coming later received none. Palliation is all that can be expected of roentgen treatment, but there was undoubted prolongation of life in certain cases.—E. H. Q.

Skin and Subcutaneous Tissues

Pedunculated Fibromyoma of the Inguino-Abdominal Region. Bachhuber, C. A. [Coll. of Med. Evangelists, Los Angeles, Calif.] *Am. J. Surg.*, **61**:308-309. 1943.

Case report.—W. A. B.

The Mode of Origin of Tumors. Solitary Localized Squamous Cell Growths of the Skin. Willis, R. A. [Alfred Hosp., Victoria, Australia] *Cancer Research*, **4**: 630-644. 1944.

The structure of a series of early, localized squamous cell carcinomas of human skin is described, including the dermal as well as the epidermal changes.

The structure of these growths is incompatible with a strict unicentric view regarding their origin, but shows instead that each has arisen by spreading cancerization of a field of epidermis. Such cancerization usually commences from a single central focus, but several initial foci may be present.

The precancerous state of an area of skin includes significant dermal changes, especially in the subepithelial elastic tissue, and invasion of the dermis by the cancerous epithelium probably commences at points of greatest damage of the dermal elastica.

Progressive neoplasia in a field of tissue does not imply the passage of any carcinogenic stimulus from cell to cell, but is merely the progressive response of an area of epithelium to the same original stimuli, a response graded according to the gradients of the effective stimulation.—Author's summary.

Nervous System

Meningioma of Thirty Years' Duration. Report of a Case. Cloward, R. B., and Kepner, R. D. [Honolulu, T. H.] *Arch. Neurol. & Psychiat.*, **50**:327-334. 1943.

A case report. The slow growth of the tumor was due to its type and location, the extensive, radical removal of bone at the first operation, and the postoperative roentgenotherapy. The series of complications that followed the removal of the recurrent tumor are discussed.—M. E. H.

Multiple Meningiomas. Removal of Four Tumors from Region of the Foramen Magnum and Upper Cervical Region of the Cord. List, C. F. [Univ. of Michigan, Ann Arbor, Mich.] *Arch. Neurol. & Psychiat.*, **50**: 335-341. 1943.

Case report and a discussion of the surgical management of multiple meningiomas.—M. E. H.

Fever as the Presenting Symptom of Brain Tumor. Brodsky, B., Cohen, L., and Gray, I. [Coney Island Hosp., Brooklyn, N. Y.] *New York State J. Med.*, **44**:628-630. 1944.

A report of a case in which fever was present for 8 weeks as the chief manifestation of a meningioma of the sphenoid ridge. The importance of ophthalmoscopic examination as a part of the diagnostic armamentarium of the internist is shown.—J. L. M.

Metastasizing Intracranial Tumors. Dublin, W. B. [Fort Steilacoom, Wash.] *Northwest Med.*, **43**:83-84. 1944.

This purports to be the fifth reported case of extracranial metastasis of a malignant meningeal tumor. No clinical data are given. Three tumor nodules were found in the pleura, but the exact location is not stated; a single tumor mass was situated in the meninges of the right occipitoparietal region. All tumors are said to have had the same histological appearance. Photographs of the cells forming the meningeal tumor alone are included, and the description states that collagenous tissue was sometimes abundant. No proof is offered that the cerebral rather than a pleural mass represented the primary tumor.—E. E. S.

Tetraplegia Relieved by Removal of Cord Tumor. Ecker, A., [Syracuse Univ. Coll. of Med., Syracuse, N. Y.] *New York State J. Med.*, **44**:1245-1247. 1944.

A case report.—J. L. M.

Eye

Treatment of Retino-Blastoma. Radiation Therapy Supplementing Surgical Treatment. Tice, G. M., and Curran, E. J. [Univ. of Kansas Sch. of Med., Kansas City, Kans.] *Radiology*, **42**:20-33. 1944.

Treatment of retinoblastoma by surgery alone gives a poor survival rate. When there is bilateral involvement, if surgical treatment saves the patient's life it condemns him to total blindness. In this series of 20 cases, half the tumors were bilateral. Fifteen patients received radiation therapy supplementing surgery, and 7 of these are living. Because of the frequency of extension of the tumor along the optic nerve, routine implantation of radium adjacent to the optic nerve stump is considered logical. Radium implantation of the second eye when there is bilateral involvement has been used in the earlier cases, but the use of external x-ray therapy is now considered more satisfactory.—R. E. S.

Female Genital Tract

Twisted Ovarian Cysts in Children. Fowlie, J. A. [Santa Rosa, Calif.] *Am. J. Surg.*, **64**:285-287. 1944.

Case report.—W. A. B.

Operative Behandlung des Ovarialkarzinoms. [Operative Treatment of Ovarian Carcinoma.] SIEBKE, H. *Wien. klin. Wchnschr.*, 1942, 2. Abstr. in *Schweiz. med. Wchnschr.*, **72**:929. 1942.

Every ovarian tumor should be extirpated because of the probability that it is already malignant, or will ultimately become so.—W. H. W.

A Rare Ovarian Tumour (Brenner Type or Adenoacanthoma?) SIMPSON, J. C., and BRANCH, A. [St. John, N. B.] *Canad. M. A. J.*, **50**:437-439. 1944.

Case report.—M. E. H.

Malignant Granulosa Cell Tumor: Case Report. BANKS, T. V. [Dyersburg, Tenn.] *J. Tennessee M. A.*, **37**:81-82. 1944.

The tumor developed in a 17 months old infant, the signs and symptoms simulating those of acute appendicitis. There was uneventful recovery following resection of the growth. The report is made because of the unusual occurrence at this age.—E. E. S.

Luteinized Granulosa Cell Tumor of the Ovary (Luteoma). GIORDANO, A. S., and HAYMOND, J. L. [South Bend Med. Lab., South Bend, Ind.] *Am. J. Clin. Path.*, **14**:28-33. 1944.

Case report with 5 figures.—J. G. K.

Thecoma of the Ovary Associated with Pleural Effusion and Ascites; Meigs Syndrome. PERLMUTTER, M. [Long Island College Hosp., Brooklyn, N. Y.] *Ann. Int. Med.*, **20**:132-140. 1944.

Case report.—J. G. K.

Adrenal-Like Ovarian Tumor Associated with Cushing's Syndrome (So-Called Masculinovoblastoma, Luteoma, Hypernephroma, Adrenal Cortical Carcinoma of the Ovary). KEPLER, E. J., DOCKERTY, M. B., and PRIESTLEY, J. T. [Mayo Clinic, Rochester, Minn.] *Am. J. Obst. & Gynec.*, **47**:43-62. 1944.

A case is reported of adrenal-like ovarian tumor associated with Cushing's syndrome. Surgical removal of the tumor resulted in regression of most of the signs and symptoms. Three years after the operation the patient was in good health. Data from 13 similar cases collected from the literature are tabulated. The theory that these tumors originate from adrenal cortical rests seems a logical one to the authors, although other explanations have not been ruled out.—A. K.

The Blood Vessels of the Myomatous Uterus. FAULKNER, R. L. [University Hosp., and Western Reserve Univ. Med. Sch., Cleveland, Ohio] *Am. J. Obst. & Gynec.*, **47**:185-197. 1944.

The distortions in the blood vessels of the uterus caused by myomatous tumors and the intrinsic vessels of the tumors themselves were studied by anatomical methods. The view that most myomas contain a mass of proliferating arteries but few or no veins was confirmed. A rich capillary bed emptying toward the periphery of the tumor probably exists. No evidence of blood entering and leaving a myoma by arterial channels was found. Free arteriovenous anastomoses were encountered 4 times in 60 specimens but probably were in tumors injured at operation. Even overinjection did not fill lymphatics in or around myomas.—A. K.

The Management of Carcinoma of the Corpus Uteri. CORSCADEN, J. A. [New York, N. Y.] *New York State J. Med.*, **44**:986-991. 1944.

The most important factor in improving the results of treatment for carcinoma of the corpus will be the shortening of the interval between the appearance of the first symptom and the administration of treatment. This interval is still discouragingly great. Of the 201 cases here studied, one-third of the patients had symptoms for more than a year, and half of them for more than 6 months before the first visit to a physician.

The best treatment for carcinoma of the corpus is a combination of radium, x-ray, and operation. Room for improvement lies in the technic of radium application and in the selection of the order in which the three therapies shall be given.—J. L. M.

Adenocarcinoma of the Body of the Uterus Arising from a Benign Endometrial Polyp: Report of a Case. FERRIS, D. O., and DOCKERTY, M. B. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:133-136. 1944.

A brief review of the literature and a discussion of the criteria for deciding whether a carcinoma originates in a benign endometrial polyp. A case report is presented with photomicrographs of a polyp showing typical adenocarcinoma.—J. L. M.

Demonstrationsstunde für Aerzte. 3. Massnahmen zur frühzeitigen Diagnose des Kollum-Karzinoms. [Demonstrations for Physicians. Early Diagnosis of Cancer of the Cervix Uteri.] LABHARDT. *Schweiz. med. Wchnschr.*, **72**:928. 1942.

In spite of all instruction 60% of the patients come too late for cure by either surgery or radiotherapy. Hence cancer campaigns must be intensified (radio).

Practitioners are urged to submit every suspicious case to the most searching examination (biopsy), and not to prescribe ergot for a bleeding woman and send her away without an examination.

As about 25% of women with carcinoma of the cervix do not bleed from it, it is highly desirable that every woman over 25 be examined on principle 3 or 4 times a year.—W. H. W.

Leukoplakie und Karzinom. [Leukoplakia and Carcinoma.] TREITE, P. Zentralbl. f. Gynäk., **40**:(page not given). 1942. Abstr. in *Schweiz. med. Wchnschr.*, **72**:1454. 1942.

The histological findings in 50 women were carefully compared with the clinical and colposcopic findings, and the patients watched for years thereafter. The author reaches the following conclusions: Leukoplakia is a symptom, not a diagnosis, and just as little a histologically definable entity. It appears whenever light is reflected from a thickened horny layer through which the red of the blood vessels in the connective tissue papillae no longer shows.

Ten years' observation does not support the dictum that leukoplakia leads inevitably to carcinoma. Leukoplakia is sometimes already carcinoma, but not necessarily so, and may never terminate in carcinoma. It follows, therefore, that not every leukoplakia of the cervix justifies amputa-

tion, and that only biopsy is capable of furnishing a conclusive diagnosis.—W. H. W.

Die Kolposkopie, die Diagnose, und die Therapie des Portiokarzinoms. [Colposcopy and the Diagnosis and Treatment of Cancer of the Cervix.] Stöckel, W. *Zentrlbl. Gynäk.*, **40**:(page not given). 1942. Abstr. in *Schweiz. Med. Wchnschr.*, **72**:1454. 1942.

Colposcopy discloses early changes in the cervical epithelium, but by itself can never replace biopsy. Simple amputation of the cervix may not be adequate even for early carcinomas as a wholly superficial one may creep upward along the cervical canal.

In general the writer prefers radiation for the favorable and the inoperable cases, and total vaginal extirpation for the intermediate group, though admitting that in exceptionally skillful hands the results of radiation are almost or quite as good.—W. H. W.

Ueber die Behandlungserfolge beim Carcinoma colli uteri. [Results of Treatment in Carcinoma of the Cervix Uteri.] Müller, J. H. [Universitäts-Frauenklinik Zürich, Zürich, Switzerland] *Schweiz. med. Wchnschr.*, **72**:909-910. 1942.

Of 137 women with carcinoma of the cervix, 130 were treated: with combined radium and roentgen therapy (109), with surgery and postoperative radiation (14), or with surgery alone (7). For various reasons 7 remained untreated.

Though in most of the cases the carcinoma was inoperable when first seen, at least a 5 year cure was achieved in 40.8%.

The author emphasizes the fact that cancer of the cervix is not necessarily a disease of advanced age, for many of his patients were between 20 and 50 years old.

Contrary to popular belief the prognosis was no worse in the younger women than in the older.—W. H. W.

Primary Malignancies of the Vaginal Wall. Two Case Reports. Furman, J. [Fort Worth, Texas] *Texas State J. M.*, **39**:335-336. 1943.

Less than 1% of all malignant growths in women are primary in the vaginal wall. In the 2 cases reported here, much scar tissue had been left in the vaginal walls after excessive trauma at childbirth.—J. L. M.

Male Genital Tract

Benign Hypertrophy of the Prostate. A Morphological Study. Moore, R. A. [Washington Univ. Sch. of Med., St. Louis, Mo.; New York Hosp., and Cornell Univ. Med. Coll., New York, N. Y.; Western Reserve Univ., Cleveland, Ohio; and Anatomisch-pathologisches Institut des Krankenhauses der Stadt Wien] *J. Urol.*, **50**:680-710. 1943.

This is a comprehensive article written from the pathologist's viewpoint. Seven hundred and eighty-two prostates obtained at autopsy and 31 organs obtained from operations were examined by step sections not over 4 mm. in thickness. Forty-seven other operative specimens were studied with selected sections, and 1 prostate was cut in full serial section.

A review of the literature shows that the incidence of prostatic hypertrophy at autopsy increases progressively with age, but the frequency of patients requiring surgery is maximal in the seventh decade. The author wonders if the destruction of the internal sphincter is not the main cause of beneficial results from prostatectomy rather than the bulk of tissue removed. Marital state and sexual drive can not clearly be associated with the disease. The Chinese are less affected than members of the white or black races. The incidence of the disease does not vary with the varying frequency of goiter as reported from various cities here and in Europe. Anthropometric studies on patients with prostatic hypertrophy are urgently needed.

On the basis of his studies the author concludes that the first histologically demonstrable change is a hyperplasia of the stroma. Rarely is epithelial hyperplasia primary. The periurethral tissue is most commonly involved. The anterior and posterior lobes are only rarely involved. The cell in hypertrophy has a relative decrease in secretory activity while the stroma shows a relative increase in muscle and absence of elastic tissue. Lymphoid tissue does occur in the prostate and is often mistaken as indicative of inflammation. Selective arteriosclerosis as a cause of the condition could not be demonstrated. Inflammation is not the cause of benign hypertrophy. Carcinoma only rarely develops in a nodule of benign hypertrophy. Surgical specimens are valueless for the study of the relation of the origin of benign and malignant conditions because the whole gland is not available. Recurrence after operation may be due to growth of nodules not removed or to development of new nodules. Thirty text figures and an extensive bibliography are included.—V. F. M.

Development of Carcinoma of the Prostate Following Prostatectomy. Greene, L. F., and Thompson, G. J. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:76-80. 1944.

The goal of prostatectomy is the restoration of normal micturition. By none of the three surgical approaches, suprapubic, perineal, or transurethral, is the entire prostate gland removed. Two cases are presented in detail, and 5 cases are cited from the records of the Mayo Clinic, to illustrate the fact that carcinoma can appear many years after suprapubic or perineal prostatectomy. Among 8 additional cases recorded at the Mayo Clinic, it appeared that a diagnosis of carcinoma was made after an average of 16 years subsequent to suprapubic prostatectomy.—J. L. M.

Regression of Lymph Node Metastases after Orchidectomy and Stilbestrol in Carcinoma of the Prostate: Report of a Case. Graves, R. C., and Cross, J. [Pondville State Hosp., Walpole, Mass.] *J. Urol.*, **51**:59-63. 1944.

Bilateral orchidectomy plus stilbestrol therapy caused a marked regression of metastases in cervical and inguinal nodes. Four months after orchidectomy a small inguinal node was removed for follow-up biopsy; it was found to contain chiefly fibrous tissue, but some tumor tissue was still present. The patient was clinically well at the end of 7 months and had gained 20 pounds.—V. F. M.

Union of Pathologic Fracture of Femur Following Castrations for Carcinoma of the Prostate. Middleton, A. W. [Univ. of Utah Med. Sch., Salt Lake City, Utah] *Am. J. Surg.*, **64**:144-146. 1944.

Case report.—W. A. B.

Evaluation of Sex Hormones in the Treatment of Benign Prostatic Hypertrophy, Carcinoma of the Prostate and Other Diseases of the Genito-Urinary System. Heckel, N. J. [Coll. of Med., Univ. of Illinois, Chicago, Ill.] *J. Clin. Endocrinol.*, **4**:166-172. 1944.

Twenty-four patients with prostatic carcinoma were treated with diethylstilbestrol for from 6 to 34 months. Medication consisted in most instances of 3 mgm. of the estrogen daily, taken orally in 3 divided doses. In addition to endocrine treatment transurethral resection was carried out in 19 of the patients, suprapubic cystotomy in 1 patient. Clinical evidence of improvement was noted in 58% of the cases; 17% received no benefit; 25% of the patients died during the course of treatment. As judged by rectal palpation, prostatic tissue became softer and smaller in many of the cases that were improved under estrogen therapy, but in no instance was a normal status believed to have been obtained. No untoward side-effects of treatment were noted.

The results obtained with estrogenic treatment of 33 men with benign hypertrophy of the prostate were unsatisfactory—J. B. H.

The Treatment of Cancer of the Prostate. Huggins, C. [Chicago, Ill.] *Canad. M. A. J.*, **50**:301-307. 1944.

It is possible by reducing the amount or the activity of circulating androgens to control to some degree—often a considerable degree—far advanced prostatic cancer in large numbers of patients.—M. E. H.

Medical and Surgical Care of Hypertrophy and Cancer of the Prostate. Young, H. H. [Johns Hopkins Hosp., Baltimore, Md.] *Texas State J. Med.*, **39**:521-526. 1944.

The author presents a review of his experience in this field, which began at the turn of the century. Prostatism is so complex in its symptoms and so varied in its pathology that it can be handled satisfactorily only by careful selection of the operative procedures best suited to obtain a radical cure. The exclusive use of transurethral resection for all types of prostatic obstruction, even the very large and the malignant, is in the opinion of the author, indefensible.—J. L. M.

Discussion: Treatment of Carcinoma of Prostate. The Royal Society of Medicine, London, England. Section of Urology. *Proc. Roy. Soc. Med.*, **37**:350-358. 1944.

Mr. Clifford Morson dealt with the surgical treatment of carcinoma of the prostate. "The so-called radical operations are excision of the whole prostate and bladder base by either (a) the suprapubic route or (b) the perineal. . . . . The suprapubic and perineal excisions of cancer of the prostate are, in my opinion, unjustifiable operations." No patient in his series of radical operations, and of cases treated with radium by every known method, survived longer than 5 years, which is the expectation of life in untreated cases. "I have nothing but condemnation for castration. All it does is to cause atrophy of the seminal vesicles and normal prostatic tissue. There is no scientific evidence that a single cancer cell is destroyed. Temporary improvement in micturition is brought about by the atrophy of normal tissue in the region of the prostatic urethra. . . . . My considered opinion of the place of surgery in the treatment of this disease is that it should only be adopted for the relief of urinary obstruction. The choice lies between cystotomy, transurethral resection and ureteric transplantation into the bowel." Whatever treatment was applied to the primary growth, very few patients survived longer than 3 years.

He had seen a number of patients who had become symptom-free within a week of the beginning of treatment with stilbestrol, with absorption of the major part of the primary growth. The improvement was not always maintained. He advised in all cases, whether the diagnosis of carcinoma was or was not certain, immediate treatment with stilbestrol (3 mgm. every 4 hours) until the patient was symptom-free, when the dose could be reduced.

Professor E. C. Dodds summarized the history of (1) the treatment of carcinoma of the prostate by estrogens and (2) of the investigation of serum acid phosphatase. Between 5 and 10 units of serum acid phosphatase give a strong suspicion of carcinoma of the prostate, whilst over 10 is diagnostic. Experience has shown that higher figures are obtained in patients with metastases. Treatment with stilbestrol may be begun with 1 mgm. 3 times a day "increasing to 5 or more until the symptoms come under control. Alternatively, one can watch the progress of the treatment by the estimation of the acid serum phosphatase. Once this has been reduced to normal limits, we have been surprised at the small amount of stilboestrol required to maintain the patient symptom-free." We have not yet comparative experience of dienestrol, hexestrol, and stilbestrol. "Finally, it cannot be too strongly emphasized that no single member of the workers in this field has ever claimed that this treatment represents a cure. It would appear that a very large number of cases can be rendered symptom-free by the administration of synthetic oestrogens; as to how long this can continue it is not possible to say although cases have been maintained in perfect health for periods of over three years."

Dr. W. M. Levitt gave a summary of the radiotherapeutic treatment and of the mode of metastatic spread, of cancer of the prostate. Forty to 50 per cent of cases without known metastases improve considerably under radiotherapy. The symptoms improve until frequency and dysuria are completely, or almost completely, relieved; in many cases it would be impossible to say on rectal examination that the patient had ever had a carcinoma of the prostate. But the great majority of these gratifying results are not lasting. "In a fair proportion of cases of carcinoma of the prostate the growth can, by irradiation, be so severely damaged without undue damage to the healthy tissues and without undue risk to the patient as to lead to its apparent total regression and to paralyse its growth for a variable period." X-radiation does not act by way of castration. The speaker suggested a thorough trial of combined but not simultaneous x-ray and estrogen therapy. Persons taking estrogens appear to have a lower tolerance to x-rays.

Lieut.-Colonel W. L. Harnett had compared the expectation of life in cases of cancer of the prostate under various treatments with that of a normal population of the same age. The mean duration of life in the group treated by prostatectomy was 77% of that expected; in

those treated by "palliative methods" or by radio-therapy this percentage was 55 and in those untreated, 33.

Mr. Kenneth Walker had found subcapsular castration of great benefit in some cases.

Mr. Terence Millin had found the immediate results dramatic in about 90% of 92 cases treated by subcapsular orchidectomy, stilbestrol, or both. Only a small proportion of bony metastases disappeared. In a remarkable case numerous metastases in the pelvis disappeared. The dose of stilbestrol was usually 5 mgm. daily for 2 to 3 weeks and then 2 to 3 mgm. indefinitely. The treatment was not curative as deaths were now occurring in those treated for more than 2 years.

Mr. E. W. Riches had treated during the past year 24 patients with 15 to 20 mgm. of stilbestrol daily with favorable results; about one-half of the patients developed mastitis after 500 to 600 mgm. He showed radiograms indicating regression of pulmonary metastases in one case.

Mr. G. E. Vilvandré spoke of a man with metastases in the sacrum and spine, who was alive and working some years after receiving only a little x-radiation.

Mr. Hugh Donovan had treated 14 patients with encouraging results.

Mr. Kenneth Heritage found that symptomatic relief following the use of stilbestrol was often most dramatic, and when this treatment failed, bilateral subcapsular orchidectomy had never failed to give relief.

Dr. L. R. Woodhouse Price spoke of the value of immediate frozen sections of endoscopy material and of wet-film fixation of aspiration specimens.

Mr. J. Gabe had found stilbestrol (5 mgm. thrice daily) of value in about one-half of his cases.—E. L. K.

Plasma Acid Phosphatase in Carcinoma of the Prostate and the Effect of Treatment with Stilboestrol. Watkinson, J., Delory, G. E., King, E. J., and Haddow, A. [Royal Cancer Hosp. (Free), and British Post-Graduate Med. Sch., London, England] *Biochem. J.*, **38**:4-5. 1944.

In confirmation of Kutscher and Wolbergs (*Ztschr. f. physiol. Chem.*, **236**:237-240. 1935) and Gutman and Gutman (*Proc. Soc. Exper. Biol. & Med.*, **39**:529-532. 1938) an acid phosphatase was demonstrated in the normal adult prostate and found to be increased in the blood plasma of patients suffering from carcinoma of the prostate with metastases in the bones. No such increase occurred in the absence of metastasis to bone. Normal human semen contained large amounts of the enzyme, but very little was found in the semen of a patient with eunuchoid syndrome. In a number of cases of prostatic carcinoma with a high level of plasma acid phosphatase this returned to normal under treatment with stilbestrol.—A. H.

Tuberculoid Reaction in Seminoma. Cohen, M., and Lee, J. J. (Univ. of Pittsburgh, and Elizabeth Steel Magee Hosp., Pittsburgh, Pa.] *J. Urol.*, **50**:477-480. 1943.

On microscopic examination tubercle-like formations were found in a typical testicular seminoma. Acid fast bacilli could not be found. Tuberculoid reactions have been described in ovarian dysgerminoma, a tumor with which testicular seminoma is histologically identical.—V. F. M.

Cavernous Hemangioma of the Testicle. Morehead, R. P., and Thomas, W. C. [Bowman Gray Sch. of Med. Wake Forest Coll., Winston-Salem, N. C.) *J. Urol.* **51**:72-74. 1944.

A case of cavernous hemangioma of the testis is described. The authors believe this to be the first recorded in the literature.—V. F. M.

Carcinoma of the Spermatic Cord and Epididymis Extension from Primary Carcinoma of the Stomach. Lewis, L. G., Goodwin, W. E., and Randall, W. S. [Walter Reed General Hosp., Washington, D. C.] *J. Urol.*, **51**:75-80. 1944.

This is a complete description of a case in which carcinoma from the stomach invaded both spermatic cords and the right epididymis. The presenting sign was a scrotal mass. Autopsy indicated the mechanism of spread to be peritoneal implantation followed by direct extension down the inguinal canals.—V. F. M.

Unusual Scrotal Tumor: Report of a Case of Neurofibrosarcoma. Nation, E. F., and Potampa, P. B. [Los Angeles Co. General Hosp., Los Angeles, Calif.] *J. Urol.*, **51**:174-177. 1944.

A 7 pound scrotal tumor, histologically a neurofibrosarcoma, was removed from a patient, with a successful result over a 6 months follow-up period. The tumor was known to have been present for 6 years but had increased greatly in size during the past 12 months. Photographs of gross and microscopic specimens are included.—V. F. M.

Urinary System—Male and Female

Influence of Anilin Dyes on Urinary Tract Tumors. Rose, D. K. [Washington Univ. Med. Sch., Barnes Hosp., and Barnard Free Skin and Cancer Hosp., St. Louis, Mo.] *J. Urol.*, **51**:81-84. 1944.

A concise review of the subject.—V. F. M.

Chemical Carcinogenesis, Drugs, Dyes, Remedies and Cosmetics with Particular Reference to Bladder Tumors. Davis, E. [Univ. of Nebraska Coll. of Med., Omaha, Nebr.] *Nebraska M. J.*, **29**:41-50. 1944.

The paper gives a detailed review of the history of our knowledge concerning the production of cancer by accidental or intentional application of chemical agents. The review includes studies with coal tar derivatives, azo dyes, estrogenic substances, metallic and vegetable matter, and many miscellaneous chemical compounds. Numerous references are given to the publications concerned with carcinogenic hydrocarbons and with the bladder tumors produced by aniline dyes. With this as support, it is suggested that many of the proprietary drugs habitually consumed or applied may be important factors in the production of cancer in man especially of the bladder.—E. E. S.

Primary Osteogenic Sarcoma of Bladder. Tremblay, R. G., Crane, A. R., and Harris, A. [St. John's Hosp., Brooklyn, N. Y.] *J. Urol.*, **51**:143-148. 1944.

A 69 year old male, upon whom a diagnosis of vesical calculus had been made, was operated upon and found to have a calcified bladder tumor. Histological examination disclosed a typical osteogenic sarcoma. The diagnosis was further substantiated by chemical tests. The

patient died 4½ months later with recurrence and pulmonary metastases. The authors believe the lesion originated in remnants of the Wolffian body. Eight similar cases are recorded in the literature.—V. F. M.

Wilms' Tumor of the Kidney: A Clinicopathologic Study of Forty-four Proved Cases. Weisel, W., Dockerty, M. B., and Priestly, J. T. [Mayo Foundation, and Mayo Clinic, Rochester, Minn.] *J. Urol.*, **50**:399-413. 1943.

Forty-four instances of Wilms' tumor were observed at the Mayo Clinic between 1904 and 1940, an incidence of 1 in 25,000 patients. Twenty-nine of the tumors were in females and 15 in males. The oldest patient was 59, but the majority were 3 years of age or less. No tumors were bilateral. Involvement of the renal vein was frequent; in 4 of the 7 successfully treated cases invasion of the veins had occurred. Upon careful microscopic study, 20 of the tumors were found to contain striated muscle. Nephrectomy plus radiation is the treatment of choice. Prognosis is poor since the majority of patients die within one year, but 7 of this group of 44 survived for from 2 to 20 years. The patient who survived 20 years did not have radiation.—V. F. M.

Adenoma of the Kidney with Associated Lesions. Report of Three Cases. Bugbee, H. G. [New York, N. Y.] *J. Urol.*, **50**:389-397. 1943.

Three instances of benign renal adenoma are described and illustrated. The finding in each case was incidental, nephrectomy having been done for hydronephrosis, pyonephrosis, and tuberculosis respectively.—V. F. M.

Leiomyoma of the Urethra (Female). Ratner, M., and Strasberg, A. [Jewish General Hosp., Montreal, Canada] *Canad. M. A. J.*, **50**:439-440. 1944.

Case report. Tumors of the female urethra are relatively rare, and this is the first report of a leiomyoma of this organ in the female.—M. E. H.

Oral Cavity and Upper Respiratory Tract

Cancer of the Lip. A Study of Fifty-Six Five-Year Cases. Whitcomb, C. A. [Jeanes Hosp., Philadelphia, Pa.] *Am. Jour. Surg.*, **63**:304-315. 1944.

Of 56 patients studied, all were men; 55 cancers arose from the lower lip, one from the upper. The squamous cell carcinomas were graded according to Broders' method: grade I, 32 cases; grade II, 17 cases; grade III, 5 cases; and grade IV, no case; two cancers were not graded. Of patients with metastases, 15% survived 5 years following surgical, x-ray, or radium therapy, singly or combined, and 83% of the 36 who never had metastases lived 5 years.—W. A. B.

Carcinoma of the Lip at the New Haven Hospital, 1921 to 1940, Inclusive. Lawrence, E. A., and Oughterson, A. W. [Yale Univ. Sch. of Med., New Haven, Conn.] *Connecticut State M. J.*, **8**:353-357. 1944.

During the last decade there has been great improvement in the treatment of cancer of the lip due to improved therapy and to the fact that patients present themselves earlier for treatment. Treatment by radium moulage yields a high percentage of successful results. Routine dissection of the neck is not justified and is unnecessary unless clinical cancer is evident in the lymph nodes.

A summary of 113 cases is presented.—M. E. H.

Mixed Tumor of the Lip. Report of Two Cases, Including One of Mixed Tumor of the Lower Lip. Hamrick, J. G., and Howe, J. S. [Medical Coll. of Va., Richmond, Va.] *Arch. Path.*, **37**:143-146. 1944.

The growths were of salivary gland type and contained epithelial cell nests and cords, and myxomatous and cartilaginous tissues. Histologically and clinically they were nonmalignant. Brief reference is made to 87 previously reported cases of mixed tumors of the lip, of which 5 arose from the lower lip.—J. G. K.

Das Zungenkarzinom. [Carcinoma of the Tongue.] Seifert, E. [Würzburg, Germany] *Med. Welt*, **14**. 1942. Abstr. in *Schweiz. med. Wchnschr.*, **72**:1109. 1942.

General principles. Fullest cooperation between surgeon and radiologist is to be desired.—W. H. W.

Secondary Carcinoma of the Mandible. An Analysis of Seventy-One Cases. Buirge, R. E. [University of Minnesota, Minneapolis, Minn.] *Surgery*, **15**:553-564. 1944.

An analysis of 71 cases. The operative mortality among 57 cases of resection of the mandible for advanced carcinoma was 17.5%. Of 47 patients who survived operation, 31.9% lived 3 years; 19.3%, 5 years; and 12.8%, 8 years.—W. A. B.

Rhinoscleroma. Kellert, E. [Ellis Hosp., Schenectady, N. Y., and W. B. Plunkett Memorial Hosp., Adams, Mass.] *New England J. Med.*, **229**:647-650. 1943.

Rhinoscleroma is a chronic granuloma of the upper respiratory tract, rare in this country but not uncommonly seen in central Europe, Italy, and Egypt. Frequently cancer or tuberculosis is the initial clinical diagnosis. The case reported is illustrated with photomicrographs.—C. W.

Tumors of the Nose and Nasopharynx. Eggston, A. A. [New York, N. Y.] *New York State J. Med.*, **43**:2403-2412. 1943.

Tumors primarily of nasal and nasopharyngeal origin are discussed. As the result of years of experience, the author has gained the distinct impression that in the treatment of these tumors, whether malignant by position or intrinsically, radical surgery has too frequently been replaced by radiation. It appears that, in so far as possible, radical removal in these difficult locations should always be undertaken regardless of cosmetic results; surgery should be supplemented by the most intelligent use of radiation for the individual case.—J. L. M.

Carcinoma of the Nasopharynx. Thompson, C. M., and Grimes, E. L. [Philadelphia General Hosp., Philadelphia, Pa.] *Am. J. M. Sc.*, **207**:342-348. 1944.

Clinical-pathological discussion, with presentation of 17 cases.—J. G. K.

Papillomatosis of the Larynx in Childhood. Ferguson, C. F., and Scott, H. W. [Childrens Hosp., and Harvard Med. Sch., Boston, Mass.] *New England J. Med.*, **230**:477-482. 1944.

A clinical report of 15 cases (incidence about 1 case per 1,000 clinic patients) and a brief review of the sub-

ject. Papillomas are the commonest tumors of the larynx in childhood and should always be considered in the differential diagnosis of chronic hoarseness. Although histologically benign, they grow extremely rapidly and exhibit an extraordinary tendency to local recurrence. The mortality from laryngeal papilloma in children under 5 equals and possibly exceeds that of carcinoma of the larynx in adults. Recommended treatment is outlined.—C. W.

Salivary Glands

Tumors of Salivary Gland Origin. So-Called Mixed Tumors. Robbins, G. F. [New York Post-Graduate Med. Sch. and Hosp., New York, N. Y.] *Surgery*, **14**:924-930. 1943.

Report on 56 mixed tumors.—W. A. B.

Mixed Tumor of the Parotid Gland (The Finley Hospital Clinico-Pathologic Conferences). Nesler, A. B. [Dubuque, Iowa] *J. Iowa M. Soc.*, **34**:276-279. 1944.

A case report. Because mixed tumors of the parotid gland behave unexpectedly, the modern concepts of them are reviewed. Early complete removal would seem to prevent recurrence.—M. E. H.

Clinical Observations and Surgical Experiences with Parotid Tumors. Trueblood, D. V. [Seattle, Washington] *West. J. Surg.*, **52**:109-118. 1944.

Report of 9 cases. The simple enucleation of a lump from the parotid is not the procedure of choice, since the tumors tend to recur. The entire parotid gland should be removed without permanent damage to the facial nerve.—M. E. H.

Intrathoracic Tumors—Lungs—Pleura

The Present Position of Thoracic Surgery. Brock, R. C. [Guy's Hosp., and Brompton Hosp., London, England] *Brit. Med. Bulletin*, **2**:33-36. 1944.

A review, one section of which deals with pneumonectomy in bronchial carcinoma.—E. L. K.

Diagnosis of Intrathoracic Tumors. McCorkle, R. G., and Koerth, C. J. [San Antonio, Tex.] *Texas State J. Med.*, **39**:194-197. 1943.

A general discussion of the diagnosis of intrathoracic tumors, with 12 case reports.—J. L. M.

Intrathoracic Neurogenic Tumors. Kent, E. M., Blades, B., Valle, A. R., and Graham, E. A. [Washington Univ. Sch. of Med., and Barnes Hosp., St. Louis, Mo.] *J. Thor. Surg.*, **13**:116-161. 1944.

There is an analysis of a series collected from the literature, of 105 patients with intrathoracic neurogenic tumors, giving location of the growth, histologic diagnosis, age and sex of patient, and operative therapy. In addition 18 patients seen by the authors are described in more detail. The tumors were situated most often in the posterior part of the chest; neurogenic growths are said to be the most common tumor in that region. A long bibliography is appended.—E. E. S.

Huge Intrathoracic Fibroma: Report of a Case. Clagett, O. T., and Hausmann, P. F. [Mayo Clinic, and Mayo Foundation, Rochester, Minn.] *J. Thor. Surg.*, **13**:6-15. 1944.

This is a report of the successful surgical removal of a tumor weighing 4,972 gm. that had no definite point of origin either from mediastinum or thoracic wall but was densely adherent to both. Since the patient also suffered from thyrotoxicosis it was necessary to resect adenomas of the thyroid before thoracotomy was performed. The surgical risk involved is discussed, and a classification of benign intrathoracic growths is presented.—E. E. S.

Pneumonectomy for Bronchial Carcinoma. Laird, R. *Proc. Roy. Soc. Med.*, **37**:87. 1944.

Description of a case.—E. L. K.

Seven-Year Cure in a Case of Carcinoma of the Bronchus. Fermont, D. A. [Mount Vernon Hosp., Middlesex, England] *Brit. M. J.*, **1**:845. 1944.

Biopsy showed squamous cell carcinoma, which was treated by insertion of radon seeds.—E. L. K.

Der Bronchial- und Lungenkrebs. Häufigkeit, pathologische Anatomie und Aetiologie. [Carcinoma of the Lungs and Bronchi. Frequency, Pathological Anatomy, and Etiology.] Wegelin, C. [Pathologisches Inst. Bern, Bern, Switzerland] *Schweiz. med. Wchnschr.*, **72**:1053-1063. 1942.

A good review, with an extensive bibliography.

Though carcinoma of the lung has been reported at the age of 16 months, it is most common in the 50 to 70 age group. Its increased incidence is caused by aging of populations.

It originates most often in a bronchus. Our knowledge of its etiology is inadequate and rests upon insecure foundations. Despite the increase of smoking among women, no change in the ratio of occurrence for the two sexes (3 to 4 men to 1 woman) has been observed.—W. H. W.

Die Klinik des Bronchial- und Lungenkrebses. [Diagnosis and Prognosis of Bronchial and Pulmonary Cancer.] Staehelin, R. [Medizinische Universitätsklinik Basel, Basel, Switzerland] *Schweiz. med. Wchnschr.*, **72**:1063-1067. 1942.

No one of the symptoms is pathognomonic, since many are caused by complications. Diagnosis is attempted, therefore, by roentgenological examination or by bronchoscopy, but in spite of all modern aids in a large institution the diagnosis in the author's series of 115 cases was correct, or nearly so, in but 63%. Early diagnosis was seldom achieved.

When certain statistically unsuitable cases are omitted, only 56% of the patients lived for 6 months after appearance of the first symptoms, 27% for 1 year, and 7% for 2 years or more. One patient lived for 10 years under repeated radiations; autopsy revealed chronic pneumonia with nests of cancer cells still present.—W. H. W.

Bronchialkrebs und Lungenkrebs. [Bronchial and Pulmonary Carcinoma.] Schinz, H. R. *Schweiz. med. Wchnschr.*, **72**:1067-1070. 1942.

This disease is more common in the higher age periods, and the increasing frequency with which it is reported is a result of the aging of populations. It is much more common among men, for some reason yet unknown. The author does not think that the greater frequency in males is referable to exogenous causes such as smoking.

Among 45 patients the diagnosis was correct in 41 (89%).

Temporary palliation was achieved by radiotherapy in 42% of the cases, in the sense that life became more bearable, but there were no cures, and the author closes with the statement that carcinoma of the lung is the worst of all carcinomas in respect to treatment.—W. H. W.

Primary Carcinoma of the Lung. A Review of Thirty Proven Cases. Freedman, L. M. J., Jacox, H. W., and Alley, R. G. [Western Pennsylvania Hosp., Pittsburgh, Pa.] *Penn. Med. J.*, **47**:455-460. 1944.

Forty-five cases of lung cancer registered in the Tumor Clinic of the Western Pennsylvania Hospital from 1936 to 1942 are reviewed for evaluation of diagnostic procedures and therapeutic results. These cases represent an incidence of roughly 2% of all malignant growths seen in the clinic. Thirty proved cases are summarized. Early diagnosis is a result of early thorough investigation of suggestive symptoms.

Chest x-ray findings are not pathognomonic of lung carcinoma but serve to focus attention on lesions demanding further study. Aspiration needle biopsy, with proper preparation and care, is a valuable diagnostic procedure in the 30% of cases not suitable for bronchoscopic biopsy.

Roentgen therapy is of definite value in producing symptomatic relief, although no appreciable increase in life expectancy is obtained.—J. L. M.

Carcinoma of the Lung in a Ten Year Old Negro Boy. Halpert, B., and Russo, P. E. [Univ. Hosps., and Univ. of Oklahoma Sch. of Med., Oklahoma City, Okla.] *Arch. Path.*, **37**:290-293. 1944.

Case report.—J. G. K.

Primary Cancer of the Lungs. Mitton, K. L., and Hardisty, N. M. [New York Hosp., New York, N. Y.] *Am. J. Roentgenol.*, **51**:555-563. 1944.

A statistical study of 260 cases of cancer of the lung, cared for at New York Hospital since 1932, is presented, with detailed data on 100 of these in which the diagnosis was confirmed histologically. The value of various diagnostic procedures is analyzed. In 62 patients coming to autopsy, the locations of metastases are tabulated. The principal clinical problem is early diagnosis. Radical surgery is the method of choice for treatment, however the results even in the group so treated are not encouraging.—E. H. Q.

Plasmocytoma of the Lung. Gordon, J., and Walker, G. [N. Y. State Hosp. for Incipient Pulmonary Tuberculosis, Ray Brook, N. Y.] *Arch. Path.*, **37**:222-224. 1944.

Case report.—J. G. K.

Fibroadenoma of the Lung. Scarff, R. W., and Gowar, F. J. S. [Middlesex Hosp., London, England] *J. Path. & Bact.*, **56**:257-258. 1944.

Two cases of tumor of the lung discovered fortuitously at autopsy presented the appearance of intra-canalicular fibroadenoma of the breast. The authors draw an analogy between this tumor and pulmonary chondroma.—L. W. P.

Dermoid Cysts and Teratomata of the Mediastinum. A Review. Rusby, N. L. [London Chest Hosp., Victoria Park, England] *J. Thor. Surg.*, **13**:169-222. 1944.

There is a brief historical review. The clinical and pathologic findings in 6 patients having such tumors are presented with a study of 174 cases found in the literature. Various theories concerning pathogenesis are discussed. The greater part of the article is devoted to a summary of the clinical features of these tumors. A long list of references of case reports is included.—E. E. S.

Mediastinal Lipoma. A Case Report. Watson, W. L., and Urban, J. A. [Memorial Hosp., New York, N. Y.] *J. Thor. Surg.*, **13**:16-29. 1944.

The tumor weighed 6.8 lbs. and is said to be the largest mediastinal lipoma successfully excised from the chest cavity and reported in the literature. Contrast visualization of the thoracic blood vessels and heart showed extreme displacement. Six months after operation the mediastinum had returned to normal position, there was radiographic evidence of fibrosis and contracture in the left hemithorax, but the left lung had not re-expanded. No evidence of oxygen absorption by the left lung was obtained.—E. E. S.

Mesothelioma of the Pleura. Postoloff, A. V. [Univ. of Toronto, Toronto, Canada] *Arch. Path.*, **37**:286-289. 1944.

A striking feature of the tumor in the case here reported was the presence of an osteoid matrix.—J. G. K.

Heart

Myxome microscopique de la cloison chez une fillette de trois mois, bloc auriculo-ventriculaire 3/1. [Microscopic Myxoma of the Septum in a Three Months Old Girl with Auriculo-Ventricular Block 3/1.] Mahaim, Y., Schweiz. Gesell. f. Inn. Med., Tenth Ann. Meet., Lausanne, May 9-10, 1942. Abstr. in *Schweiz. med. Wchnschr.*, **72**:1392. 1942.

Report of a small myxoma on the right side of the septum membranaceum with severe damage to the His-Tawara bundle.—W. H. W.

Primary Sarcoma of the Heart. Tedeschi, C. [Medfield State Hosp., Harding, Mass.] *Arch. Path.*, **37**:70-77. 1944.

Report of a case in a 68 year old white man who died suddenly following the rapid onset of cardiac decompensation. Four figures show the polypoid tumor formations in the wall of the right atrium, the infiltration of the myocardium by immature mesenchymal cells, and the argentaffin fibers in close relation to the cells of the growth.—J. G. K.

Liver

Primary Carcinoma of the Liver Combined with Tuberculosis and Diabetes Mellitus. Joynt, G. H. C. [Queen Alexandria Sanatorium, London, Canada] *Canad. M. A. J.*, **50**:529-534. 1944.

Case report. The occurrence of hypoglycemia and hyperglycemia in liver disease is briefly discussed.—M. E. H.

Cancer of the Liver in the Negro in Africa and in America. Kennaway, E. L. [Royal Cancer Hosp. (Free), London, England] *Cancer Research*, **4**:571-577. 1944.

Such data as are available suggest that the very high incidence of primary cancer of the liver found among Negroes in Africa does not appear among Negroes in the United States, and is therefore not of a purely racial character. Hence the prevalence of this form of cancer

in Africa may be due to some extrinsic factor, which could be identified. The statistical evidence on this question is confused by the inclusion of cancer of the gall bladder in the same category with cancer of the liver.—Author's summary.

Carcinoma of the Gall Bladder. A Clinical and Pathologic Study. Vadheim, J. L., Gray, H. K., and Dockerty, M. B. [Mayo Clinic, Rochester, Minn.] *Am. J. Surg.*, **63**:173-180. 1944.

A report of 77 cases of primary carcinoma of the gall bladder removed surgically. Stones were present in 88% of the cases. The site of origin of the carcinoma, determined in 48 cases, was in the region of the fundus in 54%, in the midportion in 27%, and in 19% at the neck. Direct extension beyond the wall of the gall bladder or visible metastases were present in 48 cases (64%) of the 75 cases in which these factors were ascertained. The percentage of metastases varied with the histological grade (Broders' index) of the lesion: Grade I, 25% of 20 cases; Grade II, 64% of 25 cases; Grade III, 88.8% of 18 cases; and Grade IV, 100% of 12 cases. In 75 cases microscopic examination showed 64 (85.3%) of the carcinomas were adenocarcinomas, 2 (2.7%) were of the squamos cell type, and 9 (12%) were mixed adenocarcinoma and squamous cell carcinoma (adenoacanthoma). There were 5 year cures in 45% of cases of carcinoma, Grade I, in 4.3% of cases of Grade II, and none in other groups.—W. A. B.

Peritoneal and Retroperitoneal Tumors

Malignant Disease of the Peritoneum. Berghausen, O. [Cincinnati, Ohio] *Ohio State M. J.*, **39**:1115-1116. 1943.

A very brief presentation of the spread of malignant tumors over the peritoneal surfaces, and the clinical picture thus created.—E. E. S.

Retroperitoneal Teratoid Tumors in Infancy and Childhood. Arnheim, E. E. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **10**:355-364. 1943.

The two most common retroperitoneal tumors occurring in infancy and childhood are neuroblastoma sympatheticum and embryoma of the kidney. Their differentiation from retroperitoneal teratoid tumors is described. The author reports a case of teratoid tumor in an infant 3 months of age, this being the fourth case in infancy or childhood in which the tumor has been successfully removed. A transperitoneal liberal incision is the best approach for the removal of these tumors. Twenty-three cases reported in the literature are reviewed.—A. Cnl.

Liposarcoma. Report of a Case. Daly, J. [Fort Worth, Tex.] *Texas State J. Med.*, **39**:332-334. 1943.

Liposarcomas are rare tumors, most commonly found in the region of the buttocks and retroperitoneal spaces. They grow slowly, are encapsulated, tend to recur at a higher degree of malignancy, and have a most unfavorable prognosis. Treatment is directed toward a wide excision. The value of x-rays is debatable. One case of the retroperitoneal variety is presented.—J. L. M.

Recurring Retroperitoneal Fibromyxosarcoma. Dixon, C. F., and Vadheim, J. L. [Mayo Clinic, and Mayo Foundation, Rochester, Minn.] *Minnesota Med.*, **27**:203. 1944.

The authors present a case in which a retroperitoneal fibromyxosarcoma adherent to the vena cava was removed. After living comfortably for 8 years, the patient returned with a recurrent lesion that also was adherent to the vena cava in the identical region. It was possible to remove the sarcoma with excellent result a second time.—J. L. M.

Retroperitoneal Tumors. Hoch, G. F. [New York, N. Y.] *J. Urol.*, **51**:128-131. 1944.

Three case reports of neurogenic sarcoma, adrenal carcinoma, and calculus pyonephrosis respectively.—V. F. M.

Retroperitoneal Cavernous Hemangioma. Millman, M. [Springfield, Mass.] *J. A. M. A.*, **124**:773-774. 1944.

Case reported because of the large size of the tumor, its extrarenal origin, and its rather unusual clinical picture and course.—M. E. H.

Surgical Removal of Huge Retroperitoneal Epithelial Cyst with Adenocarcinoma Originating in the Lining. Nolan, L. E., and Laird, W. R. [Laird Memorial Hosp., Montgomery, W. Va.] *Am. J. Surg.*, **64**:405-411. 1944

Case report.—W. A. B.

Bone and Bone Marrow

Classification of Bone Tumors. Caldwell, G. T. [Dallas, Tex.] *Texas State J. Med.*, **39**:282-285. 1943.

The author presents a classification of bone tumors, based upon that of Geschickter and Copeland under the 3 main headings of benign tumors of bone, malignant bone tumors (including tumors of bone marrow) and metastatic tumors of bone and bone marrow. The various groups under these headings are discussed briefly.—J. L. M.

Diagnosis in Primary Bone Tumors. Carrell, W. B. [Dallas, Tex.] *Texas State J. Med.*, **39**:289-290. 1943.

A brief presentation of the problem.—J. L. M.

Indications for Surgery in Bone Tumors. Coley, B. L. [Dallas, Tex.] *Texas State J. Med.*, **39**:290-293. 1943.

A general discussion.—J. L. M.

Interinnomino-Abdominal Amputation for Chondrosarcoma and Extensive Chondroma: Report of Two Cases. Ghormley, R. K., Henderson, M. S., and Lipscomb, P. R. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:193-199. 1944.

A brief review of the literature and 2 case reports.—J. L. M.

Case Report with Roentgen and Pathological Findings Before and After Curettage and Roentgen Therapy with Amputation for Sarcoma. Giant-Cell Tumor of the Lower Femur. Mandeville, F. B., and Howe, J. S. [Richmond, Va.] *Radiology*, **42**:56-63. 1944.

A case is reported in which first curettings showed benign giant cell tumor of the lower femur. Postoperative radiation was given, but there was recurrence with sarcomatous changes 3 years after treatment. The patient is living and well 5 years after amputation.

A bibliography of 69 references is appended.—R. E. S.

Osteogenic Osteolytic Sarcoma of the Os Pubis. Friedman, S. T. [Jewish Memorial Hosp., New York, N. Y.] *Am. J. Surg.*, **64**:248-253, 1944.

Case report.—W. A. B.

Multiple Metatarsal Fractures Associated with Osteogenic Sarcoma. MEYERDING, H. W. [Mayo Clinic, Rochester, Minn.] *J. A. M. A.*, **124**:228-230. 1944.

A report of a case representing a 13 year cure of osteogenic sarcoma with multiple metatarsal fractures.—M. E. H.

A Case of Plasma-Cell Myelomatosis with a Large Renal Metastasis and Widespread Renal Tubular Obstruction. NEWNS, G. R., and EDWARDS, J. L. [E. M. S. Hosp. and County Lab., Stafford, England] *J. Path. & Bact.*, **56**:259-262. 1944.

Report of a case, with postmortem findings. Several bones were involved. An extensive foreign-body giant cell reaction in the renal tubules was attributed to the albuminous casts present, associated with myelomatous infiltration of the renal tubules. Metastases were present also in the subcutaneous tissues.—L. W. P.

MUSCLE AND TENDON

Rhabdomyosarcoma. Case Report. DANCIGER, J. A., and WARREN, J. [Univ. of Tennessee, Sch. of Med., Knoxville, Tenn.] *J. Pediat.*, **19**:223-228. 1941.

The tumor, which developed in the region of the gastrocnemius of the right leg, was first noticed when when the child, a negro boy, was 6 months old. Growth of the tumor was progressive until death of the boy at the age of 2 when clinical signs indicated lung metastases. Autopsy revealed diffuse infiltration of both lungs and extensive invasion of pleural surfaces by pedunculated masses.—A. C.

Xanthoma of Tendon Sheath. CRISTOL, D. S., and GILL, A. B. [Mayo Clinic, Rochester, Minn., and Univ. of Pennsylvania Med. Sch. and Hosp., Philadelphia, Pa.] *J. A. M. A.*, **122**:1013-1014. 1943.

A case is reported illustrating the difficulties in the diagnosis and treatment of this condition.—M. E. H.

Large Xanthoma of Knee Joint. FAHEY, J. J. [Chicago, Ill.] *Proc. Inst. Med. Chicago*, **15**:132-133. 1944.

Case report. Xanthoma is the most common type of benign tumor arising from the synovial membrane of a joint. The presence of either a palpable mass or soft tissue tumor demonstrable by x-ray, and the aspiration of sanguineous brown or yellow fluid with a high cholesterol content are aids in diagnosis.—M. E. H.

Hemangioma of Joints. COBEY, M. C. [War Department Manuscript Board] *Arch. Surg.*, **46**:465-468. 1943.

Report of 4 cases.—W. A. B.

Hemangioma of the Synovial Membrane of the Knee Joint Cured by Synovectomy. HARMON, P. H. [Guthrie Clinic and Robert Packer Hosp., Sayre, Pa.] *Arch. Surg.*, **47**:359-363. 1943.

Report of a case.—W. A. B.

Venous Hemangioma of Skeletal Muscle. Case Report. LIGHT, R. A. [Vanderbilt Univ. Med. Sch., Nashville, Tenn.] *Ann. Surg.*, **118**:465-468. 1943.

Pain was the chief complaint in this case of venous hemangioma of the lateral head of the right gastrocnemius and was relieved by surgical extirpation of the lesion.—W. J. B.

Malignant Synovioma. STANFORD, S., and HORNE, E. A. [The General Infirmary, and Univ. of Leeds, Leeds, England] *J. Bone & Joint Surg.*, **25**:883-891. 1943.

Only about 25 reported cases of malignant tumors arising from synovial membrane can be regarded as authentic. The tumor described by these authors arose in the knee of a 16 year old boy and in the early stages simulated an inflammatory process. Exploration later established the neoplastic nature of the lesion and disclosed infiltration of muscle and fascia but not of bone. Despite mid-thigh amputation metastases appeared in lung and tracheobronchial lymph nodes. The tumor in the knee was undifferentiated and resembled, in many respects, a neuroblastoma.—E. E. S.

Angioma of the Tibialis Anterior. A Case Report. ZADEK, I. [New York, N. Y.] *J. Bone & Joint Surg.*, **25**:930-931. 1943.

Symptoms present for at least 9 years were due to a tumor that could be recognized only by exploration. The patient was aged 14 at the time of resection. Pain, which had been excruciating, disappeared promptly, and there was good return of function.—E. E. S.

Desmoid Tumor. JUDD, D. B., and MASSON, J. C. [Mayo Foundation, and Mayo Clinic, Rochester, Minn.] *Minnesota Med.*, **27**:279-280. 1944.

A case report of a patient with a large desmoid tumor 18 cm. in diameter and weighing 2,550 gm. An unusual feature was the rapid growth of the tumor.—J. L. M.

BLOOD VESSELS

Hemangio-Endothelioma: A Tumor of Blood Vessels Featuring Vascular Endothelial Cells. STOUT, A. P. [Columbia Univ., and Presbyterian Hosp., New York, N. Y.] *Ann. Surg.*, **118**:445-464. 1943.

The author feels that there are probably 3 forms of malignant vascular tumors: hemangiopericytoma, a vascular form of leiomyosarcoma, and hemangioendothelioma. The criteria given for diagnosing hemangioendothelioma are: atypical endothelial cells in greater abundance than necessary for the formation of a simple endothelial lining, and the presence of anastomosing vessels with an outer reticulin framework. Silver staining is of great help in diagnosis. Chorionepithelioma and hypernephroid carcinoma are apt to be confused with hemangioendothelioma. The existence of a benign metastasizing hemangioma is not substantiated. A discussion of the literature and 18 case reports of hemangioendotheliomas are included in the paper. Eleven of the patients reported on were females, and 7 were males; 3 were colored; 9 were less than 30 years of age; 6 were more than 50 years of age at the time of onset; 10 died with metastases.—W. J. B.

LEUKEMIA, LYMPHOSARCOMA, HODGKIN'S DISEASE

Congenital Leucemia. Report of Two Cases. CROSS, F. S. [Lansing, Mich.] *J. Pediat.*, **24**:191-194. 1944.

The 2 cases reported are of interest because of the congenital features in both and the unusual skin manifestations in one. A review of the literature for the last 25 years reveals 20 cases of congenital leukemia, 16 myelo-

genous, 3 lymphogenous, and 1 questionable in type.—M. E. H.

A Case of Acute Leukemia Complicating Pregnancy, With Necropsy Findings in the Fetus. Applebaum, H. S. [Mt. Sinai Hosp., Cleveland, Ohio] *Ohio State M. J.*, **40**:536-537. 1944.

The disease was discovered during the sixth month of pregnancy and proved fatal following Caesarian section in the eighth month. The fetus was found dead, and necropsy revealed the absence of leukemic cells in the fetus as would be expected.—E. E. S.

Chronic Lymphatic Leukemia. Report of Two Cases. Richardson, C. R. [Clifton Springs, New York] *New York State J. Med.*, **44**:292-294. 1944.

The first case is reported because of the extreme degree of lymphocytosis and the paucity of clinical symptoms until a few days before admission to the hospital and up to a few weeks prior to death. In the second case sulfadiazine was effectively used in the treatment of a coexisting pneumonitis but had little or no effect on the lymphoid cell proliferation.—J. L. M.

Osteosclerosis, Myelofibrosis and Leukemia. Churg, J., and Wachstein, M. [Mt. Sinai Hosp., New York, N. Y.] *Am. J. M. Sc.*, **207**:141-152. 1944.

A discussion, based upon a study of 97 cases of leukemia, 6 of which showed a varying degree of myelofibrosis without osteosclerosis. A review of the literature shows that osteosclerosis is often associated with nonleukemic myelosis and only rarely if ever with true leukemia.—J. G. K.

Adrenal

Hormonal Tumors of the Adrenal. Fifteenth Annual William T. Belfield Memorial Lecture. Cahill, G. F. [New York, N. Y.] *Proc. Inst. Med. Chicago*, **15**:66. 1944.

Tumors of the adrenal may be cortical or medullary and in either location may be hormonal or nonhormonal. Diagnosis is made by a study of symptoms, identification of excess hormone excreted in the urine, demonstration of a pressor substance in the blood that disappears under the effects of ergotamine, and the change in the adrenal by air insufflation x-rays.—M. E. H.

The Hormonal Tumors of the Adrenal Gland. Cahill, G. F. [Presbyterian Hosp., New York, N. Y.] *Pennsylvania M. J.*, **47**:655-667. 1944.

A general discussion.—J. L. M.

Pancreas

Surgery of the Pancreas. Cole, W. H. [Univ. of Illinois Coll. of Med., Chicago, Ill.] *Surg. Clin. North Am.* **24**:16-28. 1944.

In this general discussion a brief section deals with the clinical manifestations, diagnosis, and treatment of carcinoma.—J. L. M.

Partial Duodenopancreatectomy in One Stage for Carcinoma of the Head of the Pancreas: Report of a Case with Successful Outcome. McCall, C. H., and Waugh, J. M. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **19**:147-152. 1944.

A brief review of the literature followed by a detailed report of a case and a discussion of fat metabolism in patients in whom the pancreatic juices have been excluded from the intestine.—J. L. M.

Hyperinsulinism. A Report of the Surgical Treatment of Three Patients. Bell, H. G., Craig, L. S., and McCorkle, H. [Univ. of California Med. Sch., San Francisco, Calif.] *Surgery*, **15**:681-692. 1944.

Report of 3 cases with removal of islet cell tumors from the region of the tail of the pancreas in two.—W. A. B.

Pineal

The Pinealoma: Its Relationship to Teratoma. Russell, D. S. [Bernhard Baron Inst. of Pathology, London Hosp., London, and Nuffield Department of Surgery, Oxford, England] *J. Path. & Bact.*, **56**:145-150. 1944.

The author advances evidence, based on 4 original cases and a consideration of several in the literature, that the majority of pineal tumors are atypical teratomas. Such evidence depends on the mixed character of the tissues in certain of these tumors, in the recognition of "pinealoma" areas in manifest typical and atypical teratoma of the pineal, and in their close resemblance to the spermatoblastoma—a tumor that many regard as also an atypical teratoma.

This view is supported by the occurrence of ectopic pinealomas in the infundibulum, quadrigeminal plate, vermis, and pituitary gland.

A true pinealoma, showing a mosaic of immature pineal cells interspersed among large adult spheroidal cells, is regarded as a rare but definite entity.—L. W. P.

Thyroid

The Pathologic Changes of the Thyroid Gland. Severance, A. O., and Johns, S. [San Antonio, Tex.] *Texas State J. Med.*, **38**:717-722. 1943.

Of 148 specimens from the thyroid gland, examined at the Nix Hospital Clinical Laboratory between 1930 and 1943, 33% were neoplastic; 6.4% exhibited malignant tumors; 41%, toxic goiters. The gross and microscopic differential diagnosis of goiters, strumas, benign tumors, and the malignant tumors of the thyroid is stressed.—J. L. M.

Parathyroid Adenoma—Report of Unusual Case. Goldman, D., and Sapadin, A. [Jewish Hosp., Cincinnati, Ohio] *Ohio State M. J.*, **40**:437-439. 1944.

The presence of the tumor was suspected only on the chance finding of hypercalcemia and hypophosphatemia. There was no clinical evidence of osteitis fibrosa or of renal calculi. On removal of the adenoma, the blood values returned to normal level.—E. E. S.

Multiple Tumors

Malignant Tumor of the Interstitial Cells of the Testis with Prostatic Carcinoma. Sharnoff, J. G., and Lisa, J. R. [City Hosp., New York, N. Y.] *J. Urol.*, **50**:471-473. 1943.

A malignant adenomatoid neoplasm of the interstitial

cells of one testis was found in a patient dying of carcinoma of the prostate.—V. F. M.

Multiple Primary Carcinomas of the Gastrointestinal Tract. Sheinfeld, W. I., and Rudolph, I. [Coney Island Hosp., New York, N. Y.] *Surgery,* **15**:579-589. 1944.

Three cases are presented. In the first there was a carcinoma of the transverse colon and a second lesion in the midascending colon. The second case was characterized by squamous cell carcinoma of the esophagus and adenocarcinoma of the stomach. In the third case there was an adenocarcinoma of the stomach and an independent adenocarcinoma of the esophagus.—W. A. B.

Association of Other Malignant Tumors with Cancer of the Skin. Lombard, H. L., and Warren, S. [Massachusetts State Dept. of Pub. Health, and Harvard Cancer Comm., Boston, Mass.] *Am. J. Pub. Health,* **33**:533-536. 1943.

A study of data obtained from the state tumor clinics has led the authors to believe that there is a greater susceptibility to cancer in persons having one cancer than in the normal population. Whether this susceptibility is caused by the first cancer or is inherent in the individual is not known. There is no evidence to warrant the assumption that the presence of a skin cancer inhibits other cancers. If anything, the evidence points to the contrary.—M. E. H.

Multiple Primary Malignant Tumors and Susceptibility to Cancer. Warren, S. and Ehrenreich, T. [Harvard Cancer Comm., New England Deaconess Hosp., Boston, Mass., Westfield State Sanatorium, and Pondville Hosp. of Mass. Dept. of Pub. Health.] *Cancer Research,* **4**:554-570. 1944.

A series of 2,829 cases of cancer was studied from the standpoint of multiple malignant neoplasms; 194 cases were found, an incidence of 6.8%. When this is combined with the series previously reported by Warren and Gates, there were 3,907 cancer autopsies with an incidence of 6.0% multiple cancers. The average age of the male group with multiple malignant tumors was 65.2 years, of the female group, 56.9 years, and of the entire group 62.5 years. The average duration from the onset of the first tumor until the time of death was 2.7 years. Frequently, it was impossible to determine the interval between the malignant tumors, but when they were clearly established as successive the average interval was found to be 3.1 years. Cases of multiple malignant growths occurred more frequently than would be expected on the basis of chance alone. This greater frequency, calculated as eleven-fold, may be attributed to susceptibility or predisposition to the development of cancer in certain persons or groups of persons.

Among the multiple growths reported were 6 cases in which 4 different malignant tumors occurred, and 23 cases in which 3 malignant tumors occurred.—Authors' abstract.

Miscellaneous

Medicolegal Aspects of Trauma and Malignant Testis Tumors. Gilbert, J. B. [Schenectady, N. Y.] *New York State J. Med.,* **43**:939-945. 1943.

Litigation cases in general have been inadequately examined and reported; claims have been settled on a basis of sympathy, not science. On the basis of present knowledge no conclusion can be drawn concerning a possible etiologic relationship between trauma and cancer of the testis, but all evidence is against the assumption that one exists.—J. L. M.

Benign and Malignant Tumors of the Foot. Kulchar, G. V. [Stanford Univ. Sch. of Med., San Francisco, Calif.] *J. A. M. A.,* **124**:761-766. 1944.

Tumors of the foot, like those of the hand, differ from neoplasms elsewhere in being frequently multiple. The clinical features are, for the most part, those of neoplasms in general. The various types of tumors that may be found on the feet are discussed.—M. E. H.

Congenital Sacro-Coccygeal Tumors. Case Report of a Teratoma. Neal, M. P., and Carlisle, J. B. [Columbia, Mo., and Sedalia, Mo.] *South. M. J.,* **36**:677-678. 1943.

Case report of a teratoma in a full term female infant, who had in addition 3 lobes composing the left lung, patent ductus arteriosus, patent foramen ovale, and patent urachus.—W. A. B.

Spindle and Giant Cell Sarcoma Arising from Unidentified Precordial Bodies. Symmers, D. [Goldwater Memorial Hosp., New York, N. Y.] *Arch. Path.,* **37**:180-184. 1944.

Case report, with 5 figures.—J. G. K.

Subscapular Ossified Hematoma. Case Report. White, J. W., and Hutner, S. [Station Hosp., Camp Joseph T. Robinson, Ark.] *Am. Jour. Surg.,* **63**:124-130. 1944.

Case report.—W. A. B.

Cancer Control and Public Health

Organizing the County for Cancer Control. Neff, J. L. [New York, N. Y.] *West Virginia M. J.,* **40**:133-137. 1944.

The role of the Women's Field Army in personal contacts and education of the public is discussed. It is stated that effort must be directed also toward enlightenment of the physicians and development of facilities for treatment.—E. E. S.

An Outline of the Plan and Work of the Division of Cancer Control of the Pennsylvania Department of Health. Reimann, S. P. [Philadelphia, Pa.] Pennsylvania M. J., **47**:21-25. 1943.

The Pennsylvania plan for cancer control is outlined; its purposes, its methods, and some of its results are given. The Division of Cancer Control of the Department of Health of the Commonwealth of Pennsylvania was established in April, 1939, and began functioning in July, 1939. Tumors were declared reportable diseases. A set of questions was devised in the form of blanks to be distributed to all the physicians of the Commonwealth. In addition it was asked that a microscopic slide of every biopsy and/or tumor specimen be sent to the Division. Since the filling out of these blanks entailed time and expense, a fee of 50 cents was provided for each one properly annotated. The plan is being adopted more and more by clinics, hospital staffs, and individual physicians throughout the Commonwealth. In spite of the detailed nature of the program, the number of accessions steadily rose

from 75 the first month, and 300 the second month, to over 1,500 at the time the article was written.—J. L. M.

The Epidemiology of Cancer From the Viewpoint of the Health Officer. Levin, M. L. [Div. of Cancer Control, New York State Dept. of Health, Albany, N. Y.] *Am. J. Pub. Health,* **34**:611-620. 1944.

There is evidence that the occurrence of human cancer is in some cases attributable to the influence of specific chemical or physical agents, to an association with precancerous lesions and with other diseases, to familial factors that may be hereditary. Many of the etiological and differential factors point to possible public health applications in the form of special attention in education, in case finding, and in follow-up. It seems reasonable to forecast that in the future, cancer control programs will be guided to a greater extent than in the past by existing knowledge and by further investigation of the epidemiological characteristics of the disease.—M. E. H.

Cancer and Workmen's Compensation Acts. Industrial Health Committee. *Rhode Island M. J.,* **27**:175. 1944.

A brief outline of the legal factors determining the outcome of compensation cases involving cancer.—M. E. H.